STUDIES ON THE PATHOPHYSIOLOGY OF UPPER GASTROINTESTINAL HAEMORRHAGE

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PREFACE

As a member of the Western Infirmary Haematemesis Management Team, I became closely involved in the care of patients with peptic ulcer haemorrhage. In spite of its high persisting mortality, I realised how little was known about the underlying pathophysiology of this condition. This thesis is devoted to furthering our understanding of this common gastrointestinal problem.

Some of the studies related to in this thesis have been published and these are listed. Collaboration and advice was sought from various colleagues and these have been acknowledged. The studies described and the writing of this thesis are entirely my own work.

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ABSTRACT

This thesis has studied the pathophysiological events which accompany upper GI haemorrhage in an attempt to more fully understand its natural history. Despite the multiplicity of aggressive factors present in the upper GI tract most gastroduodenal bleeds stop spontaneously. This is surprising in view of the high acidity, proteolytic activity, vascularity and motile nature of the upper GI tract, all factors which act to inhibit haemostasis and promote haemorrhage. During investigation of this paradox I have discovered inhibition of gastric secretion and motility following simulated intraduodenal haemorrhage, events which may represent a protective physiological response to facilitate haemostasis in the adverse environment of the upper GI tract. The relatively prolonged nature of these inhibitory responses following simulated intraduodenal haemorrhage provides additional evidence to support a possible beneficial role in haemostatic defence. Further studies have suggested these inhibitory responses may also occur with intragastric bleeding. To confirm these experimental observations initial clinical studies have revealed increases in gastric pH following active peptic ulcer bleeding which may also reflect gastric secretory inhibition.

The mediation of these events has been the subject of initial investigations both in simulated and true upper GI bleeding assessing changes in GI hormones associated with gastric secretion and motility. In both study groups this has revealed a significant increase in GIP concentrations suggesting this hormone may be involved in the mediation of these inhibitory responses.

In the clinical situation where defence mechanisms break down the identification and treatment by endoscopic means of those patients at highest risk of rebleeding is important. I have demonstrated an improvement in the ability to predict rebleeding by identifying 'high risk' peptic ulcer patients with a patent vessel in their ulcer base using an endoscopic Doppler device. In these high risk patients I have shown that endoscopic heater probe therapy can provide haemostasis effectively and safely thereby altering the natural history of peptic ulcer haemorrhage.

In conclusion, improved understanding of the pathophysiological principles governing haemostasis in the upper GI tract and the effective prediction and treatment of those patients where defence mechanisms fail are likely to improve the outcome of this common gastrointestinal problem.

SUMMARY

The pathophysiological events accompanying upper GI haemorrhage are poorly understood. In an attempt to improve our knowledge of these events I have examined in this thesis the effects of simulated and true upper GI haemorrhage on gastric secretory function, gastric motility and gastrointestinal hormone release. I have also examined factors predicting rebleeding in peptic ulcers and have demonstrated how its natural history may be influenced by endoscopic therapy.

Although the local environment of the upper GI tract is haemostatically adverse, up to 80% of all upper GI bleeds stop spontaneously. This suggests the existence of local homeostatic mechanisms which may promote haemostasis despite the aggressive factors of high acidity, proteolytic enzymes, continuing peristalsis and vascularity encountered in the upper GI tract. I have investigated three of these factors - acidity, proteolytic enzymes and motility to determine how they are influenced by a simulated upper GI bleed. This work was performed initially in healthy volunteers using an experimental study method simulating an intraduodenal bleed. The effects of intraduodenal infusion of 160ml of fresh autologous venous blood on pentagastrin stimulated submaximal gastric secretion was studied. This revealed a mean inhibition of acid and pepsin output of 30% and 40%

respectively following blood infusion compared with the pre-infusion values. In a similarly designed study the effect of intraduodenal infusion of autologous venous blood on gastric emptying was performed using a double dilution liquid meal technique. Gastric emptying was significantly delayed after blood infusion compared with a control study. This inhibition of gastric secretion and motility seen after simulated upper GI haemorrhage may therefore represent a protective physiological response to facilitate haemostasis.

The effects of intraduodenal blood infusion on gastrointestinal hormones was also studied to determine any possible mediating role in these inhibitory responses. A selective increase in gastric inhibitory peptide (GIP) was seen after intraduodenal blood infusion. GIP is a duodenal polypeptide with known inhibitory effects on gastric secretion and motility in dogs. Its only confirmed physiological function in man however, relates to its insulinotropic action in glucose metabolism. The observed increase in GIP concentrations after intraduodenal blood infusion with concomitant inhibition of gastric secretion and motility may suggest a possible mediating role in these responses.

The duration of acid inhibition after intraduodenal blood infusion was studied initially up to 3 hours following duodenal blood infusion. This revealed progressive inhibition of pentagastrin stimulated

submaximal acid secretion up to 3 hours after blood infusion. The effect of a simulated upper GI bleed at 8pm on overnight gastric acidity and submaximal gastric secretion 12 hours later was also studied. Overnight gastric pH was increased after intraduodenal blood infusion compared with a control protein infusion suggesting continuing inhibition of overnight basal gastric secretion. In addition, pentagastrin stimulated submaximal gastric acid output was significantly lower 12 hours after the simulated bleed compared with the control study suggesting a persisting effect some 12 hours later.

A possible additional protective physiological response seen after upper GI haemorrhage relates to the induction of a systemic hypercoagulable state which may facilitate haemostasis. In order to document whether this observation reflects a GI mediated event or simply results from a non-specific systemic response to haemorrhage, the effect of intraduodenal blood infusion on blood coagulation parameters was measured. No effect was noted following blood infusion suggesting the latter explanation may be correct.

Intragastric blood is common to most upper GI bleeds and the effect of blood as a chemical buffer was studied in an in-vitro study to determine its buffering capacity.

A mixture of blood:gastric juice of >1 was required to raise the combined pH to above 6.0 where coagulation may be initiated.

The effect of simulated intragastric haemorrhage on gastric acid secretion, gastric motility and serum gastrin was investigated to determine whether additional inhibitory mechanisms exist. On separate days 160ml of fresh heparinised venous blood or 160ml egg-white acting as control were instilled into the stomach and the subsequent rates of gastric secretion and emptying, and the changes in serum gastrin were noted. Compared with the control protein meal intragastric blood inhibited gastric emptying and produced 70% less acid secretion. In addition, each produced a similar small increase in serum gastrin concentrations suggesting that these secretory changes could not be explained by differences in gastrin alone. These events may also indicate additional protective physiological responses initiated by gastric bleeding.

Studies were performed in patients presenting with upper GI haemorrhage to determine whether the observed changes in gastric secretory function and GI hormones after simulated upper GI haemorrhage occur in the clinical situation. In patients with endoscopic evidence of active peptic ulcer haemorrhage intragastric pH measured by a combined glass electrode for 24 hours was significantly elevated for prolonged periods compared with a control

group. These changes occurred in the absence of significant concentrations of intragastric blood suggesting an effect independent of simple blood buffering. Such responses indicate possible inhibition of gastric secretion during the active phase of upper GI haemorrhage. In addition, in patients admitted with upper GI bleeding a selective increase in GIP concentrations was seen throughout the 24 hour period in agreement with the original intraduodenal studies. These observed changes in intragastric pH and GIP concentrations agree with my original experimental findings and may represent a local physiological response to facilitate haemostasis. Future studies are required however to confirm these findings, to identify the blood based activation factor/s and to examine the role of GIP in the mediation of these responses. The identification of these apparent defence mechanisms in the upper GI tract in response to local haemorrhage may be important increasing our understanding of the pathophysiology of this common condition.

Although the majority of all upper GI bleeds stop spontaneously the minority who continue to bleed or rebleed constitute a major clinical problem particularly as the age of the presenting population increases. Improved methods of predicting those patients who rebleed is therefore of clinical relevance particularly as improved endoscopic treatment methods are developed allowing selective treatment of 'high risk' patients. A

study was performed in patients with peptic ulcer haemorrhage presenting to the Western Infirmary, Glasgow to determine the predictive value of a localised arterial signal in proximity to an ulcer base using a Transendoscopic vascular detector (TVD) which utilises Doppler ultrasound to detect pulsatile arterial flow. A positive arterial signal in relation to the ulcer base correctly predicted rebleeding in 87% of cases which was similar to that predicted by visual stigmata. The combination of visual stigmata (visible vessel) and a positive Doppler signal however, predicted rebleeding in 100% of cases suggesting the ability to identify a vessel in an ulcer base with arterial flow within may be the best predictor of patients outcome.

The natural history of peptic ulcer haemorrhage has only convincingly been altered by surgery. Endoscopic therapy however appears to offer the ideal treatment method for an increasingly elderly and unfit population although many of the available techniques have not yet been subjected to rigorous controlled clinical trials. The heater probe is an endoscopic device which from experimental studies is the safest and most effective in producing vessel coagulation. A controlled randomised trial of heater probe (HP) therapy was performed to determine whether the HP can reduce the incidence of rebleeding in peptic ulcers presenting with haemorrhage. In a study of 43 patients with haemorrhage from high-risk

peptic ulcers 22% of sham treated patients rebled while no heater probe treated patient rebled. This study suggested heater probe therapy may be beneficial in reducing the rebleeding rate in peptic ulcer haemorrhage.

These studies may improve our understanding of the pathophysiology of upper GI haemorrhage thereby providing a rational basis for therapeutic advances.

CHAPTER 1

PATHOPHYSIOLOGY OF UPPER GASTROINTESTINAL HAEMORRHAGE

1.1. INTRODUCTION

Upper gastrointestinal (GI) haemorrhage is a major cause of emergency hospital admissions accounting for approximately 30,000 new admissions each year in the UK (SCHILLER et al 1970). Due to an increasing proportion of elderly patients the mortality has remained about 10% despite significant advances in diagnostic and resuscitation techniques (ALLAN and DYKES 1976).

Although upper GI haemorrhage is a common condition we understand little of the local physiological changes which accompany it. Without a sound knowledge of the underlying pathophysiological events, treatment regimes in upper GI bleeding have been based on longstanding widely held, but often unqualified beliefs. As a consequence medical management of acute non variceal upper GI bleeding has been generally ineffective and to date no therapeutic regime has proven benefit over placebo. A better understanding of the pathophysiological changes accompanying upper GI bleeding may provide new and more rational approaches to therapy.

1.2 HISTORICAL ASPECTS OF UPPER GI HAEMORRHAGE

Peptic ulcer haemorrhage and the prognostic implications of arterial bleeding have been known since Ancient Greek times. In 400 BC Hippocrates wrote in his Aphorisms: 'Spurting haemorrhage coming from ulcers is bad news' (HIPPOCRATES 400BC). The first documented fatality

from upper GI haemorrhage may date to Roman times (AD 453) where Attila the Hun apparently succumbed to a bleeding peptic ulcer: 'An artery had suddenly burst and as Attila lay in a supine posture, he was suffocated by a torrent of blood which, instead of finding a passage through the nostril, regurgitated into the lungs and stomach' (GIBBON 1901). Although the symptoms and signs of upper GI bleeding had been recognised, there were to be no significant advances in the understanding of the pathophysiology of ulcer haemorrhage until the 19th Century.

The first clear description of the pathological characteristics of a bleeding chronic gastric ulcer came from the French pathologist Jean Cruveilhier in 1829. He describes his findings in a post-mortem study of a young carpenter who died after several upper GI bleeds:

"At the level of the lesser curve there is a deep ulceration. The edge and floor of the ulcer are cicatrised excepting at a point where there is a clot of blood elevated like a nipple: a stylet introduced into the coronary (left gastric) artery of the stomach and directed toward the end of the vessel, pushes the clot out and enters the cavity of the stomach; but on withdrawing the stylet a little and pushing it in the same direction it can be made to re-enter the vessel which was not completely severed but only cut about three-quarters of its circumference" (CRUVEILHIER 1829).

Since Cruveilhier's time the association between major peptic ulcer haemorrhage and exposed vessels in the ulcer base has been noted by several authors (ROKITANSKY 1842; TROUSSEAU 1889; OSBORN 1954). The early rigid and semi-flexible gastroscopes offered a limited view of the upper GI tract, although drawings revealed that the early endoscopists had identified the 'visible vessel' in patients presenting with upper GI bleeding (SCHINDLER 1937; AVERY JONES 1947). However, with the advent of fibreoptic endoscopy in the 1970s for the first time the source of bleeding in the upper GI tract could be accurately identified and prognostic significance attached to lesions with identifiable stigmata of recent haemorrhage (SRH) (COTTON et al 1973; FORREST et al 1974; FOSTER et al 1978) (Fig.1). The importance of a vessel in the ulcer base was again highlighted by the endoscopic identification of the 'visible vessel' (GRIFFITHS et al 1979; JOHNSTON 1984; WARA 1985). Although this is a misnomer (the underlying artery in an ulcer base being generally invisible but the protruding clot visible), recent histological studies have confirmed that the endoscopic 'visible vessel' appearance does represent a small (mean diam 0.7mm) artery (SWAIN et al 1986a).

a

b

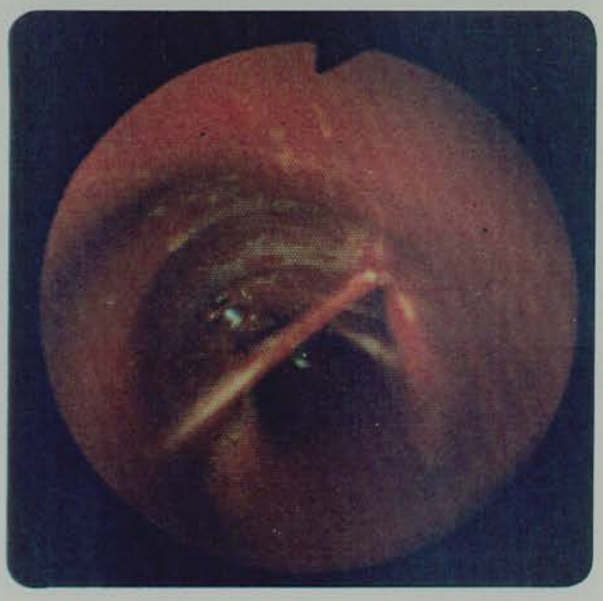


FIGURE 1

Endoscopic appearance of (a) non-bleeding visible vessel in a high lesser curve gastric ulcer and (b) the same vessel a few seconds later actively spurting.

1.3 PATHOPHYSIOLOGY OF ULCER HAEMORRHAGE

Up to 80% of all upper GI bleeds stop spontaneously (NORTHFIELD 1971) despite the haemostatically aggressive surrounding environment. This in itself may suggest the presence of specialised locally protective physiological mechanisms to promote haemostasis.

Ulcer vessel pathology

Major peptic ulcer bleeding occurs when an artery in the ulcer base is eroded (MacKAY 1954). These arteries are small (normally < 1mm) and lie in the submucosa in 60% and subserosa in 40% of cases (Fig.2). The pathological characteristics of these vessels have been documented by Swain et al in a prospective study analysing a series of 27 patients with major gastric ulcer haemorrhage who all underwent partial gastrectomy for continuing bleeding (SWAIN et al 1986a). All 27 patients had endoscopic evidence of a 'visible vessel' and histological studies confirmed a small artery (mean diameter 0.66mm: range 0.1 - 1.8mm) in 26/27 (96%) cases. The adverse prognostic significance of the endoscopic visible vessel was therefore confirmed.

Histological study confirmed aneurysmal dilation of the vessel wall in 14/27 (52%) of vessels. In addition, arteritis with polymorphonuclear cell infiltrate and fibrinoid necrosis was seen in 24/29 (83%) vessels. This

FIGURE 2 Large artery eroded in floor of a gastric ulcer with clot in lumen. This subserosal artery has been eroded flush with the ulcer base (Elastica-Van Gieson stain).

inflammation was usually localised to the vessel side closest to the ulcer floor suggesting that direct chemical attack by acid/pepsin may have been the initiating factor (Fig.3). Despite these arteries being pathological in more than 80% of cases rebleeding in Swain's series occurred in only 58% of endoscopically confirmed visible vessels. Recanalised thrombus was also seen in about 25% of cases suggesting the bleeding process was intermittent.

It is interesting that these vessels were so frequently involved by extensive arteritis and necrosis and as such would not be expected to undergo the normal haemostatic mechanisms of vessel contraction/retraction. Despite this the rebleeding rate from 'visible vessels' averages only 50% in other published series (VALLON 1981; WARA 1985), suggesting that a significant percentage of even these diseased aneurysmally dilated vessels may undergo haemostasis.

Pathological evidence therefore indicates that ulcer haemorrhage even from necrotic aneurysmal arteries may be an intermittent process suggesting the existence of locally protective mechanisms.

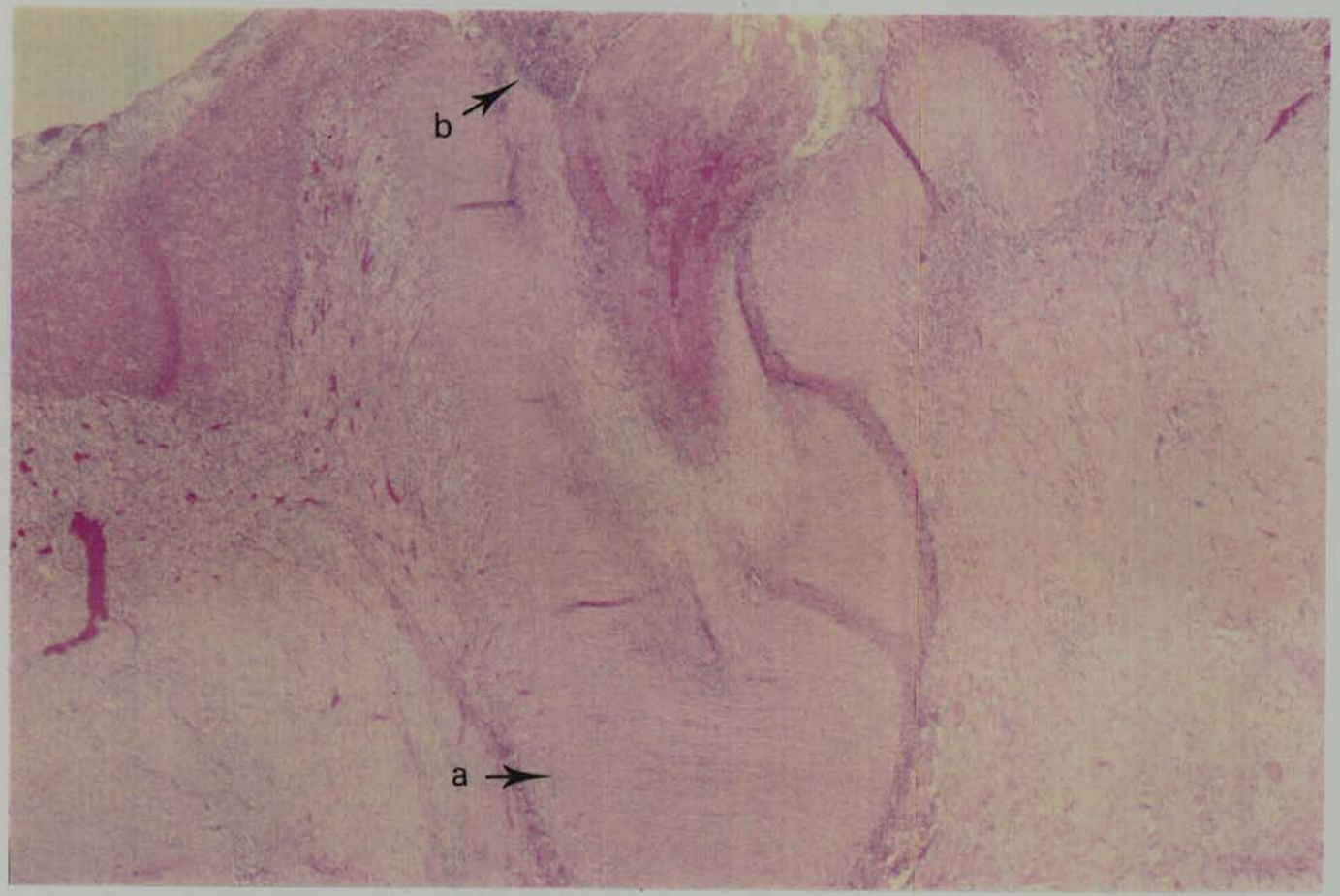


FIGURE 3 Eroded submucosal artery in a gastric ulcer base. This demonstrates (a) marked intimal thickening and (b) arteritis in the wall of the artery adjacent to the ulcer base (Haematoxylin and Eosin stain).

1.4 LOCAL FACTORS INVOLVED IN THE PATHOPHYSIOLOGY OF UPPER GI BLEEDING

1.4.1 Luminal factors

a) Gastric Acid

Gastric acid may initiate upper GI haemorrhage by its erosive effect on vessels and may potentiate bleeding by inhibiting normal blood coagulation and platelet aggregation (BODI et al 1956). The importance of gastric acid in upper GI haemorrhage relates mainly to its potent inhibitory effects on blood coagulation and platelet aggregation. These inhibitory actions depend on the free hydrogen ion activity or pH of the gastric juice as blood clotting and platelet aggregation are particularly sensitive to alteration in these parameters. Gastric mucosal haemostasis, unlike the skin or vascular system, depends primarily on processes involving the coagulation system rather than platelet aggregation (WHITTLE et al 1986) and is therefore particularly sensitive to alterations in pH.

In Vitro Studies of the effect of alterations in pH on blood coagulation and platelet aggregation

Inhibition of platelet aggregation at low pH has been found in rabbits (McLEAN & VELOSO 1967) and man (ROGERS, 1972). This effect at low pH was thought to be due to either a change in platelet shape or a

reduction in plasma factors required for aggregation. Green et al investigated the effect of hydrochloric acid on blood coagulation and platelet aggregation in an in-vitro study (GREEN et al 1978). Both blood coagulation and platelet aggregation were shown to be extremely sensitive to relatively minor increases in hydrogen ion concentration. All studies became abnormal at pH 6.8 and by pH 5.4 blood coagulation and platelet aggregation were virtually abolished. In addition previously formed platelet aggregates disaggregated at only slightly acid pH of 6.8. Similar studies by Chaimoff et al have shown that elevation of pH from acidosis to pH 7.0 induces platelet aggregation, platelet calcium and serotonin release and increases platelet factor VIII availability (CHAIMOFF et al 1978).

The fasting pH in the stomach lies between 1-2 and in the proximal duodenum between 2.2-7.0 both in normal volunteers (RUNE 1981; HANNIBAL & RUNE 1983) and in duodenal ulcer subjects (BENDTSEN et al 1987). It is surprising therefore that haemostasis should occur at all in such an adverse acidic environment.

In Vivo Studies of Gastric Acid Secretion during Upper GI Bleeding.

Gastric secretory studies were performed by Chandler and Watkinson in 105 patients presenting with upper GI bleeding in an attempt to recognise patterns of acid secretion (CHANDLER & WATKINSON 1953). An important observation was made that in patients with acute duodenal ulcers actively bleeding at the time of investigation 89% had gastric aspirates with pH > 3.5 (defined as achlorhydria) which persisted for at least 24 hours. This effect was not due to the buffering effect of blood reflux as gastric aspirates were clear in this group who had clinical evidence of continuing haemorrhage. On repeat testing some weeks later, acid secretion had returned to normal in all individuals. It is interesting to note that this temporary acid inhibition was taken as an indication for continuing medical therapy suggesting that this was a favourable prognostic factor. Although no explanation for this suppression of gastric secretion was given it was thought to represent a temporary failure of parietal cell function. A later study with increased patient numbers confirmed these patterns of acid secretion in patients presenting with upper GI bleeding (CHANDLER & WATKINSON 1959).

The observation that gastric function could be altered following an upper GI bleed has also been noted by Langman et al who found pentagastrin stimulated acid secretion to be lower in 18 duodenal ulcer subjects who had suffered a recent bleed compared with a population of uncomplicated duodenal ulcer patients (LANGMAN et al 1964). Wormsley and Grossman (1965), however, studying 117 duodenal ulcer patients showed no differences in acid secretion between two such similar groups.

Gastric secretion may be inhibited during severe shock due to sepsis or hypovolaemia presumably through splanchnic circulatory shutdown and reduced mucosal oxygen delivery (STANNARD et al 1988). It is interesting to note that Chandler and Watkinson showed a significant increase in the incidence of achlorhydria in a chronic duodenal ulcer group (who were normally hypersecretors) with a proportionate increase in the degree of shock (CHANDLER & WATKINSON 1959). Achlorhydria, however, could be attributed to shock alone in only a small proportion of cases suggesting the involvement of additional factors in reducing acid secretion.

Subsequent studies assessing gastric secretion in GI bleeding have been mainly therapeutic aimed at raising gastric pH by drug therapy on the assumption that pH is normally low in the phase of active

bleeding and that this contributes to a failure of haemostasis through inhibition of platelet aggregation and blood coagulation (CURTIS et al 1973; HASTINGS et al 1978; FIDDIAN-GREEN et al 1983; REYNOLDS et al 1987). However the limited evidence to date suggests acid secretion may already be diminished during active bleeding. The importance of pharmacological manipulation of acid secretion in the treatment of upper GI bleeding may be clearer when the accompanying local physiological responses are better understood.

b) **Pepsin**

Pepsin is a potent proteolytic enzyme found in the stomach which can initiate haemorrhage by eroding an exposed vessel wall in the ulcer base and promote rebleeding by actively digesting clot over a bleeding lesion (BERSTAD 1982).

In human gastric juice there appear to be at least 7 different pepsins (I-VII) and one non-pepsin proteinase (ETHERINGTON & TAYLOR 1967). The gastric juice from patients with chronic gastric or duodenal ulcers contains different proteolytic activity compared with juice from non-ulcer subjects (TAYLOR 1959) due to an increase in pepsin I concentrations in ulcer patients (TAYLOR 1970). Pepsin I is secreted by the fundic glands in the stomach

(ETHERINGTON & TAYLOR 1970) and has a powerful collagenolytic action up to five times greater than pepsin III which is the major constituent of normal gastric juice (ETHERINGTON et al 1980).

The mucus/bicarbonate barrier is an important part of the protective defence mechanisms of the gastro-duodenal mucosa (ALLEN & GARNER 1980). It is likely that in a bleeding peptic ulcer, adherent mucus and clot would provide the initial protection against acid/peptic attack and therefore reduce the risk of continuing bleeding. Pepsin has an optimum pH range of 1.0-3.5 using protein as substrate where pepsin I-III function at maximum rates (PIPER & FENTON 1965). However, recent evidence has suggested that pepsin I may remain active against gastric glycoprotein at pH ranges up to 5.0 (PEARSON et al 1986). In vitro studies have also shown that the addition of pepsin increased the rate of platelet disaggregation at only modestly lowered pH (4.7-7.8) (GREEN et al 1978). Therefore, it seems that pepsin may retain its ability to break down the mucus barrier and disaggregate platelets at pH values up to 5.0. It is evident therefore, that in relation to upper GI bleeding acid/pepsin attack may continue until gastroduodenal pH is above 5 and will be abolished only at pH values approaching 6.

c) **Fibrinolysis**

The intermittent nature of upper GI haemorrhage may result from cyclical temporary haemostasis with clot formation followed by fibrinolysis, clot disruption and rebleeding. This alteration between clot formation and lysis depends on the presence in the upper GI tract of both potent activators and inhibitors of proteolysis. The gastrointestinal mucosa is rich in plasminogen activator (COX et al 1967) and there is evidence to suggest that local release of this activator may induce fibrinolysis and rebleeding (COX et al 1969; NILSSON et al 1975a). In addition gastric pepsin and pancreatic proteases may also induce fibrinolysis and clot digestion (LOW et al 1980). Low et al (1980) studied the in-vitro fibrinolytic activity of human gastroduodenal juice using a 125I-fibrin clot lysis technique and found that pepsin was approximately 100 times more active against fibrin than pancreatic trypsin, chymotrypsin or elastase. In addition gastric juice was 50 times more potent in fibrinolytic terms than the same volume of duodenal juice. Gastroduodenal secretion amounts to 2-3L per day under normal conditions therefore their exists a large reservoir of potential fibrinolytic activity in the upper GI tract.

Limited studies of antifibrinolytic agents in upper GI haemorrhage have suggested possible therapeutic benefit (CORMACK et al 1973; BIGGS et al 1976; STAEL von HOLSTEIN et al 1987). It appears therefore that haemostasis in the upper GI tract may depend on the interaction between lytic activity (plasminogen activators ± peptic activity ± pancreatic enzyme activity) and clot formation. Preliminary studies have suggested enhanced fibrinolytic activity in gastric juice of patients with upper GI bleeding compared to non-bleeding patients (NILSSON et al 1975b; BUHR et al 1978; WHEATLEY et al 1987). Whether this enhanced fibrinolytic activity may account for the small proportion of patients who rebleed is unknown.

1.4.2 Mural Factors

a) **Vascularity**

The upper GI tract is highly vascularised receiving up to one fifth of the total cardiac output and the mucosa receives about 70% of this visceral blood supply through an extensive anastomotic network within the bowel wall (GUTH 1977; KONTUREK 1979). The net result is a highly vascularised mucosal circulation which usually has a close functional link with gastric secretion (JACOBSON 1967; GUTH 1982). Present knowledge suggests the gastroduodenal mucosal

circulation may be capable of considerable autoregulation in response to varying physiological events (PERRY et al 1982; LARSEN & MOODY 1982; KIEL et al 1987). Such autoregulation may be mediated through arterio-venous shunts in the submucosa, which could allow rapid shifting of large amounts of blood from one region of the stomach to another.

In the event of ulcer bleeding the outcome depends on both the size of the bleeding vessel and the ability of local mechanisms to produce haemostasis. Although the vessels involved in ulcer haemorrhage are usually pathological and therefore incapable of normal haemostatic responses, up to 68% stop bleeding spontaneously (WARA 1985). Alternative protective responses contributing to haemostasis may involve alterations in mucosal blood flow as this is clearly capable of considerable autoregulation under other physiological conditions. Such alterations in mucosal blood flow may also involve changes in gastric secretion as both parameters usually change in parallel (PIQUE et al 1988).

It is now well established that the splanchnic circulation may be altered by GI hormonal mediation. Several GI hormones have known stimulatory or inhibitory action on gastric mucosal blood flow (CHOU et al 1984). GI hormones with a known inhibitory effect on gastro-duodenal mucosal

blood flow include somatostatin (SONNENBERG & WEST 1983; PRICE et al 1985), neurotensin (FLETCHER et al 1985) and secretin (KONTUREK et al 1976a; FLETCHER et al 1985). Somatostatin in particular, has a profound inhibitory effect on splanchnic circulation, lowering mucosal blood flow and portal venous pressure (BOSCH et al 1981; MERKEL et al 1985). These responses have been utilised in therapeutic trials of somatostatin in peptic ulcer haemorrhage, although some studies have suggested this is beneficial (KAYASSEH et al 1980; CHRISTIANSEN & YOTIS 1986; TORRES et al 1986), others have not (SOMMERVILLE et al 1985; MAGNUSSON et al 1985). It is important, however, to remember that somatostatin also has a powerful gastric anti-secretory effect and any benefits seen may simply be the result of decreased secretion.

Alterations in gastric mucosal blood flow can occur in response to varying neurohormonal stimuli and may therefore be important in considering local responses to upper GI haemorrhage.

b) **Motility**

The upper GI tract (stomach and duodenum) is highly motile during normal physiological fasting conditions participating in the migrating motor complex, which is a cyclic sequence of alternating

motor activity and quiescence (HOUGHTON et al 1988). Continuing gastro-duodenal motility, however, in the context of upper GI bleeding is likely to be detrimental haemostatically in two ways.

i) Increased vascular stress

Continuing active peristalsis may dislodge fresh clot over the bleeding site and increase intramural and intravascular pressure (BODI & KAZAL 1965). These added stresses to already breached vessels in an ulcer base may result in persisting bleeding or rebleeding. In addition powerful smooth muscle contractions may overstretch undamaged mucosal or submucosal vessels leading to vessel wall disruption and bleeding (MALLORY and WEISS 1929).

ii) Enhanced acid/pepsin digestion

The physical mixing effect of gastroduodenal peristalsis may increase the rate of acid/peptic clot digestion (BODI et al 1956) and promote rebleeding. In addition considering a duodenal bleeding source, continuing gastric motility would allow the emptying of an acid/pepsin load directly onto the bleeding site. This may interfere with haemostasis and induce clot and vessel digestion. Reduction of gastroduodenal motility during upper GI bleeding therefore seems desirable and therapeutic regimes with early feeding have

been introduced as a means of inhibiting gastric peristalsis (MEULENGRACHT 1935; AVERY JONES 1947).

The effect of gastrointestinal haemorrhage on the motility of the upper GIT is unknown, however in view of the propensity of upper GI bleeds to stop spontaneously some inhibitory effect may be expected as a means of facilitating haemostasis.

1.4.3 Systemic Factors

In upper GI haemorrhage a breakdown of local haemostasis usually occurs while systemic haemostasis remains unimpaired. Although systemic coagulation defects may occur and predispose to rebleeding these are uncommon (JONES et al 1961).

It has been recently suggested that a hyper-coagulable state is induced by upper GI haemorrhage which may act in a protective manner to promote haemostasis and thereby reduce rebleeding (BLAIR et al 1986). The authors noted a hypercoagulable response as measured by a shortening in the Biobridge Impedance Clotting Time (ICT) in patients presenting with acute upper GI haemorrhage compared with an age and sex matched control group. This effect persisted for 3-4 days before returning to normal. In a controlled study assessing the effects of blood transfusion on this hypercoagulable response, Blair

et al noted that in patients randomised to receive blood, the mean ICT was lengthened from admission values when compared to values in patients receiving no blood (BLAIR et al 1986). In addition, this alteration of the ICT by blood transfusion was accompanied by an increased transfusion requirement and rebleeding rate.

It was concluded that in upper GI bleeding hypercoagulability may be a protective mechanism to promote haemostasis which may be reversed by early blood transfusion thereby promoting the risk of rebleeding. Whether these observed changes in coagulation were specific to GI bleeding (and thus may be have been induced by blood in the gut lumen) or represented simply systemic responses to blood loss were not discussed.

It is interesting therefore that despite the multiplicity of aggressive factors in the upper GIT 80% of all upper GI bleeds stop spontaneously. This paradox strongly suggests the presence of specialised defence mechanisms to promote haemostasis.

AIMS

This thesis aims to examine the local pathophysiological events occurring during acute upper GI haemorrhage with particular reference to possible protective responses.

CHAPTER 2

THE EFFECT OF SIMULATED INTRADUODENAL HAEMORRHAGE ON GASTRIC ACID AND PEPSIN SECRETION, GASTRIC MOTILITY AND GASTROINTESTINAL HORMONES.

2.1 INTRODUCTION

Considering the adverse environment for haemostasis, it is surprising that approximately 80% of acute upper GI bleeds stop spontaneously. The resting pH of the stomach and proximal duodenum is usually less than 2 and platelet aggregation and plasma coagulation are abolished in vitro at pH values of < 5.4 (GREEN et al 1978). Gastric juice is also rich in pepsin, a potent fibrinolytic agent which rapidly digests thrombus in acid medium of pH < 4 (LOW et al 1980; BERSTAD 1982). The fact that haemostasis is usually effective in the upper GI tract suggests the presence of specialised physiological mechanisms to facilitate haemostasis in this unusual environment. In order to determine whether such mechanisms exist I have studied the effect of simulated upper GI haemorrhage on gastric acid and pepsin secretion, gastric motility and GI hormone release. The first study examined the effects of simulated intraduodenal haemorrhage on these parameters.

2.2 MATERIALS AND METHODS

Gastric secretion study

The effect of simulated intraduodenal haemorrhage on gastric acid and pepsin secretion was studied in 7 healthy volunteers (6 males, 1 female; median age 29 years, range 25-36). After an overnight (12h) fast, a size 8 duodenal tube (Viomedex) and size 14 vented Andersen gastric tube

(AN 10, HW Andersen Inc, New York, USA) were passed under fluoroscopic control into the second part of the duodenum and body of stomach respectively. This allowed simultaneous intraduodenal infusion and gastric aspiration without contamination (Fig.4). At time zero, an iv infusion of pentagastrin (Peptavlon, ICI) 0.25µg/kg/hr was commenced and continued throughout the study to stimulate submaximal gastric secretion. Following a 30 minute equilibration period, 4 x 15 minute collections of gastric juice were obtained by continuous aspiration. After this (time 90 minutes) each volunteer was blind-folded and received intraduodenally either 160ml of fresh, unclotted autologous venous blood or 160ml egg-white (which has a similar protein and carbohydrate content to blood). Intraduodenal infusions were administered in random order on separate days at least one week apart. Infusions were given as 4 x 40ml aliquots at 5 minute intervals over 20 minutes. This rate of blood infusion was chosen to approximate to the intraduodenal bleeding rate expected from an average sized vessel in a duodenal ulcer base (PROTELL et al 1976; JOHNSTON et al 1987). On each study day 40ml of venous blood was removed from each volunteer's arm every 5 minutes for 15 minutes (total volume removed = 160ml) and either directly infused into the duodenum prior to clotting (blood study day) or discarded (egg study day). Following the start of duodenal infusion, a further 4 x 15 minute gastric collections were taken

Simulated Intraduodenal Haemorrhage Model

Gastric Secretion Study

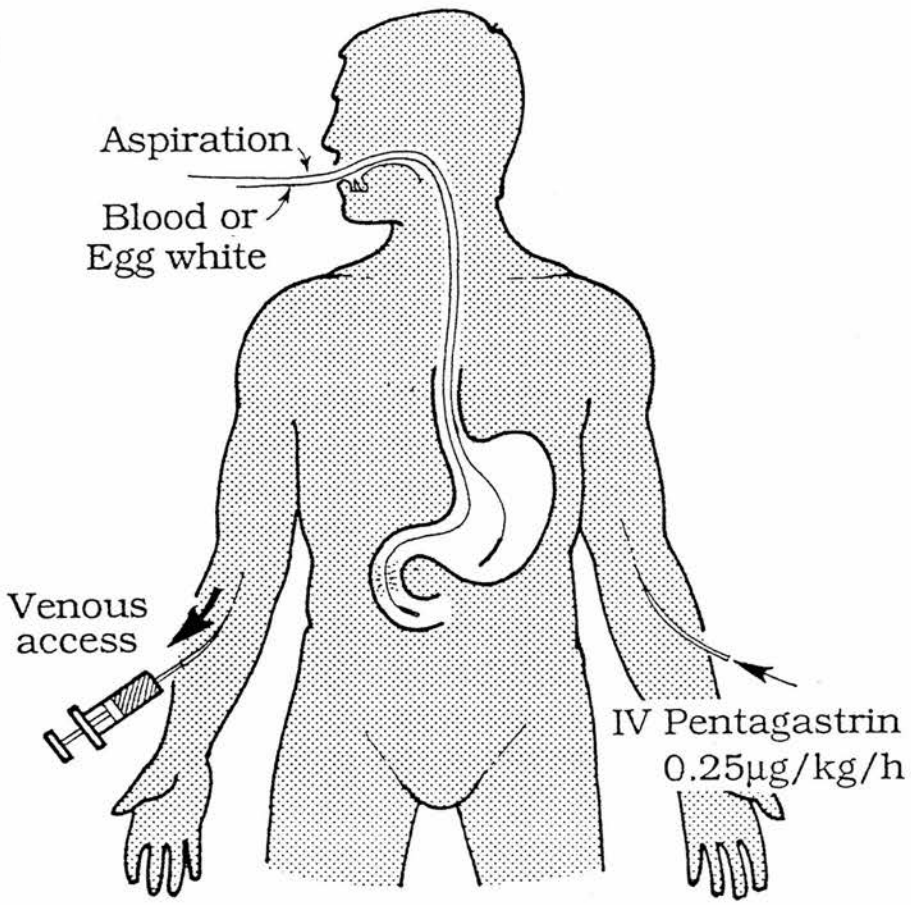


FIGURE 4

Diagramatic representation of the experimental study method illustrating the positions of the separate intragastric and intraduodenal tubes in the body of stomach and second parts of duodenum respectively. This allowed simultaneous duodenal infusion and gastric aspiration without contamination.

(90-150 min). Volumes of each 15 minute gastric aspirate were measured and aliquots retained for assay. A summary of this study method is shown in Figure 5.

Corrections were made for pyloroduodenal loss by infusing a non-absorbable marker, phenol red solution (1500mg/l) at 12ml/h intragastrically throughout the study (HOBSLEY and SILEN 1969). Corrections for duodenogastric reflux of duodenal juice were made by estimating sodium concentration of the gastric aspirate (McCLOY 1978). Microscopic blood reflux was quantitated spectrophotometrically (CRAWFORD and HOBSLEY 1968). Any study demonstrating macroscopic reflux of blood or egg-white was abandoned. Macroscopic egg-white reflux was detected visually by its effect on phenol red in the aspirated gastric juice, turning the normal acidic yellow/orange colour to pink. Four studies were repeated due to macroscopic reflux of blood in three, and egg-white reflux in one.

Gastric motility study

The effect of simulated intraduodenal haemorrhage on gastric emptying of a 600ml liquid glucose meal was studied in 6 healthy volunteers (5 males, 1 female; median age 29 years, range 25-36) using a double sampling test meal technique (GEORGE 1968).

Following an overnight fast, separate intraduodenal and gastric tubes were positioned as described above. At time zero 600ml of a liquid meal (50g dextrose diluted to

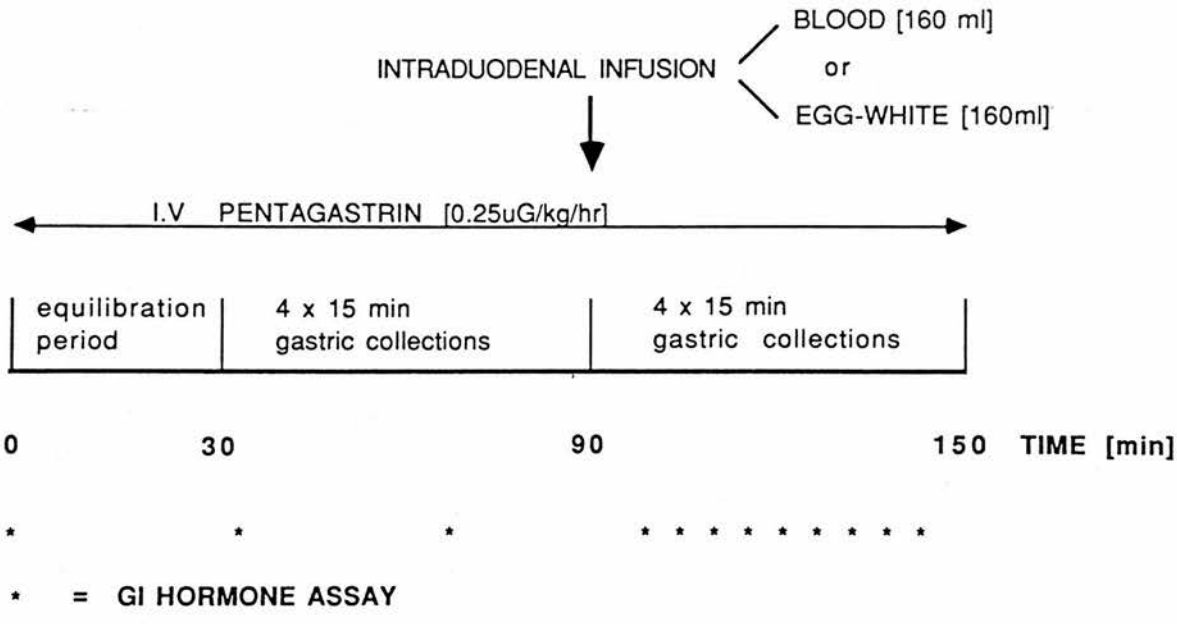


FIGURE 5

Experimental study method to determine the effects of intraduodenal blood and egg-white infusion on pentagastrin stimulated gastric secretion.

600ml in 75mmol/l NaCl with phenol red solution 45mg/l) was instilled into the stomach, mixed and 5ml aspirate kept for analysis. Each volunteer was then blind-folded and received intraduodenally either 160ml fresh autologous venous blood (4 x 40ml aliquots over 5 minute intervals as described above), 160ml egg white (4 x 40ml aliquots) or intraduodenal intubation alone in random order on separate days. At 10 minutes, 10ml of gastric aspirate was removed and kept for analysis. Immediately 10ml of phenol red solution (1500mg/l) was instilled into the stomach, the gastric contents mixed and a further 10ml gastric aliquot was kept for analysis. This double sampling technique was repeated at 10 minute intervals until time 50 minutes when the stomach was emptied completely, the volume recorded and a 10ml aliquot retained for analysis. The stomach was then washed with 100ml of water and a 10ml aliquot also retained for analysis.

Gastrointestinal (GI) hormone studies

To study possible hormonal mediation of any responses shown, serial blood samples were taken before and after intraduodenal blood and egg white infusion during the gastric secretory study.

Three basal samples were taken at 30 minute intervals before intraduodenal infusion and thereafter at 7 minute intervals until study completion at 150 minutes. Samples were added to heparinised tubes, immediately centrifuged

and plasma stored at -20 degrees Centigrade. The following GI hormones with known gastric secretory and/or motility effects were studied - gastrin, secretin, gastric inhibitory peptide (GIP), vasoactive intestinal peptide (VIP), neurotensin and somatostatin.

ANALYSIS

Gastric secretion

Gastric juice was analysed for :

1. Hydrogen ion concentration by titration to pH 7.0 with 100mmol/l sodium hydroxide.
2. Phenol red concentration by spectrophotometric absorption (Pye Unicam SP8-100 UV Spectrophotometer) at 550 and 410nm and at 410nm alone to quantitate microscopic blood reflux.
3. Sodium concentration by flame photometry (EEL Flame Photometers Ltd).
4. Pepsin concentration by Pipers method (PIPER 1960). Results were expressed as mg Sigma porcine pepsin.

GI hormones

GIP, gastrin, secretin, somatostatin, VIP and neurotensin were measured by radioimmunoassay. Details of each radioimmunoassay technique are given in the appendix.

CALCULATIONS

Acid output was expressed as total acid output in mmol/h for each hour before and each hour after duodenal infusions following correction for pyloroduodenal losses and duodenogastric reflux. Pepsin output was expressed as the total output in mg for each hour before and after intraduodenal infusions.

Intragastric volumes were calculated using the method of George (GEORGE 1968). The time taken for intragastric volume to decrease to half volume from 600ml ($t\frac{1}{2}$) was calculated in each case using linear transformation of the data.

For each GI hormone assay pre-infusion values were expressed as the mean of the 3 samples at 0, 30 and 60 minutes.

Statistical analysis

Results are given and mean ± standard error of the mean (SEM). Statistical analysis was performed using the Wilcoxon Signed Ranks test (2 sided) for paired data. Results were considered significant when $p < 0.05$.

Written, fully informed consent was obtained in each case and all studies were approved by the local Hospital Ethical Committee.

2.3 RESULTS

Gastric secretion

(a) ACID OUTPUT

Gastric acid output (mmol/h) decreased in each of the seven volunteers following intraduodenal blood infusion. The mean output being 30.0 ± 3.2 in the hour preceding intraduodenal blood infusion and 21.4 ± 3.7 in the hour following infusion ($p < 0.02$) (Fig. 6). This represented a mean reduction in acid output of 30.4% (range 16-67%) and was accounted for by a reduction in both the volume and H+ concentration of the gastric juice.

With intraduodenal egg white infusion there was no significant change in acid output being 31.8 ± 2.8 in the hour before infusion and 33.0 ± 4.4 in the hour following intraduodenal infusion (Fig.6).

(b) PEPSIN OUTPUT

Pepsin output (mg/h) decreased in each of the seven volunteers following intraduodenal blood infusion (Fig.7). The mean output being 207.5 ± 67.7 in the hour preceding intraduodenal blood infusion and 135.7 ± 54.7 in the hour following infusion ($p < 0.02$). This represented a mean reduction in pepsin output of 43% (range 19-80) and was accounted for by a reduction in both volume and pepsin concentration of the gastric juice. With

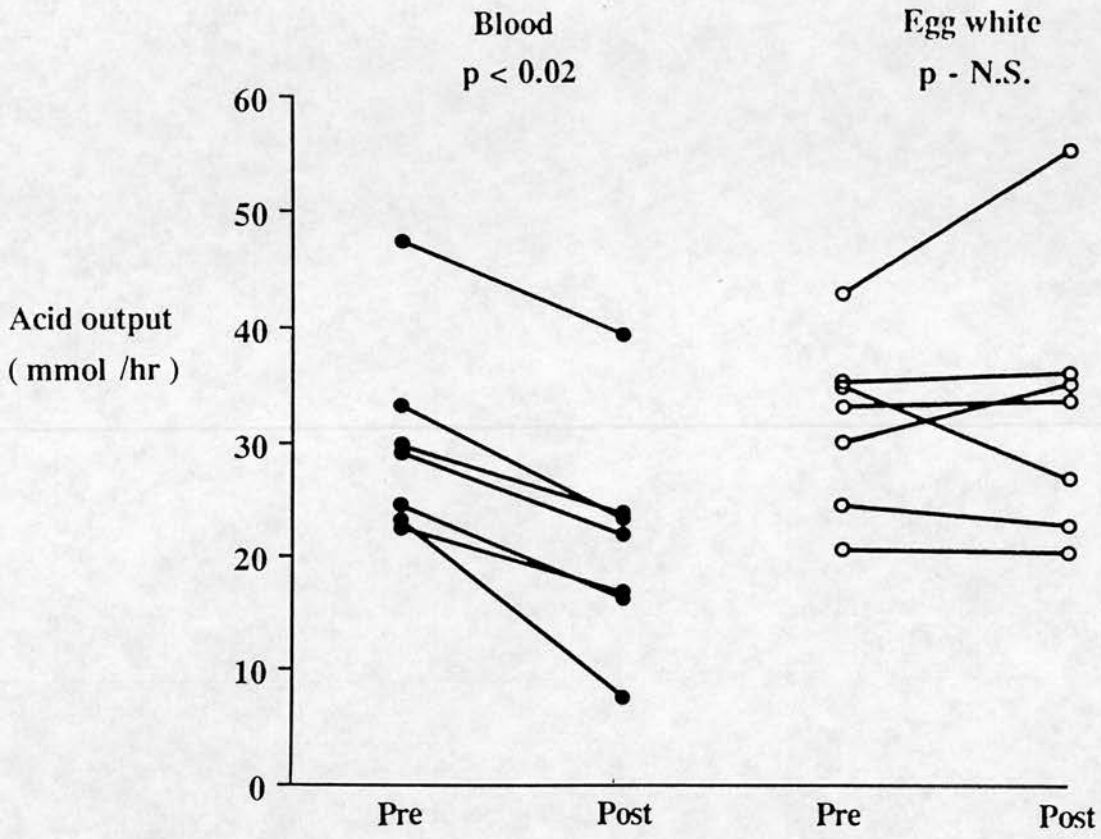


FIGURE 6

Effect of intraduodenal blood and egg-white infusion on pentagastrin stimulated gastric acid secretion in 7 healthy volunteers.

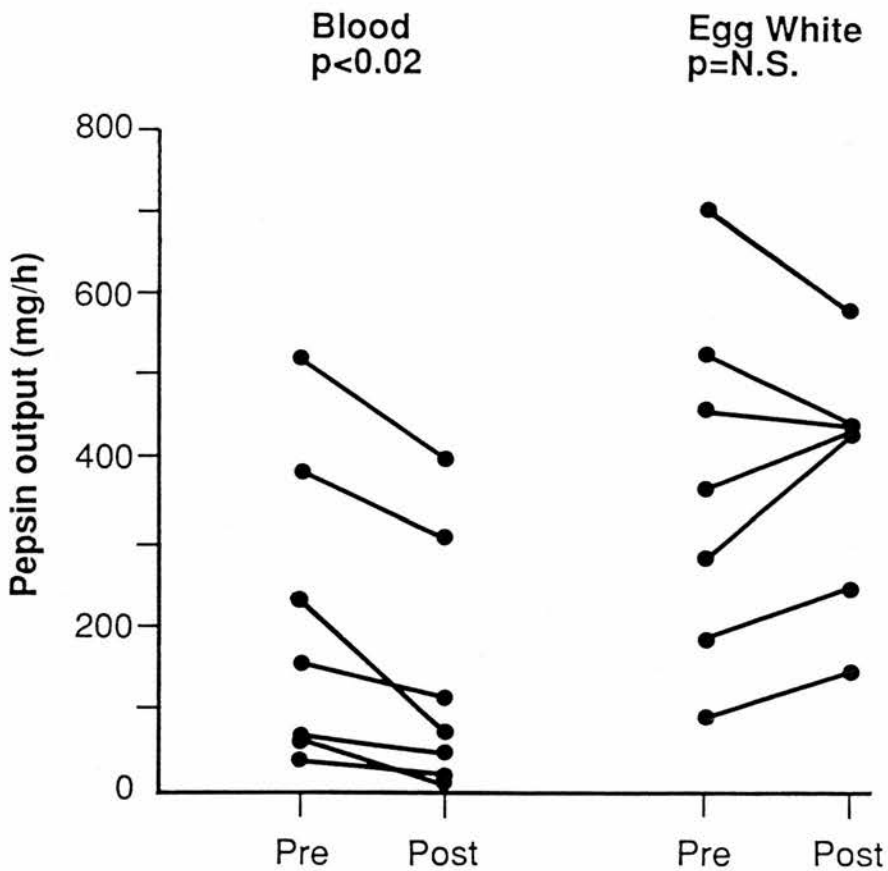


FIGURE 7

Effect of intraduodenal blood and egg-white infusion on pepsin secretion in 7 healthy volunteers.

intraduodenal egg white infusion, there was no significant change in pepsin output being 372.2 ± 82.9 in the pre-infusion hour and 376.9 ± 54.6 in the hour following intraduodenal infusion (Fig.7). Calculated recovery fractions by phenol red estimation were 91% in the blood infusion group and 94% in the egg white infusion group. The calculated mean volume of blood refluxed in the hour following intraduodenal blood infusion was 3.2 ± 0.9ml.

Gastric motility study

Gastric emptying was delayed in all 6 subjects following intraduodenal blood infusion compared with intubation alone. Figure 8 shows the residual gastric volumes with intraduodenal blood infusion compared with the control study (duodenal intubation alone). The emptying time (min) for the initial intragastric volume (600ml) to decrease to half volume ($t\frac{1}{2}$) was increased to 75.0 ± 8.2 following intraduodenal blood infusion compared with 35.5 ± 6.6 in the control study ($p < 0.02$). After blood infusion 355 ± 18ml remained in the stomach at 50 minutes, compared with 211 ± 28ml following the control study ($p < 0.02$).

Compared with intubation alone, intraduodenal egg white infusion also resulted in a delay in gastric emptying although this was less marked than following blood infusion. $T\frac{1}{2}$ (min) following egg white infusion was

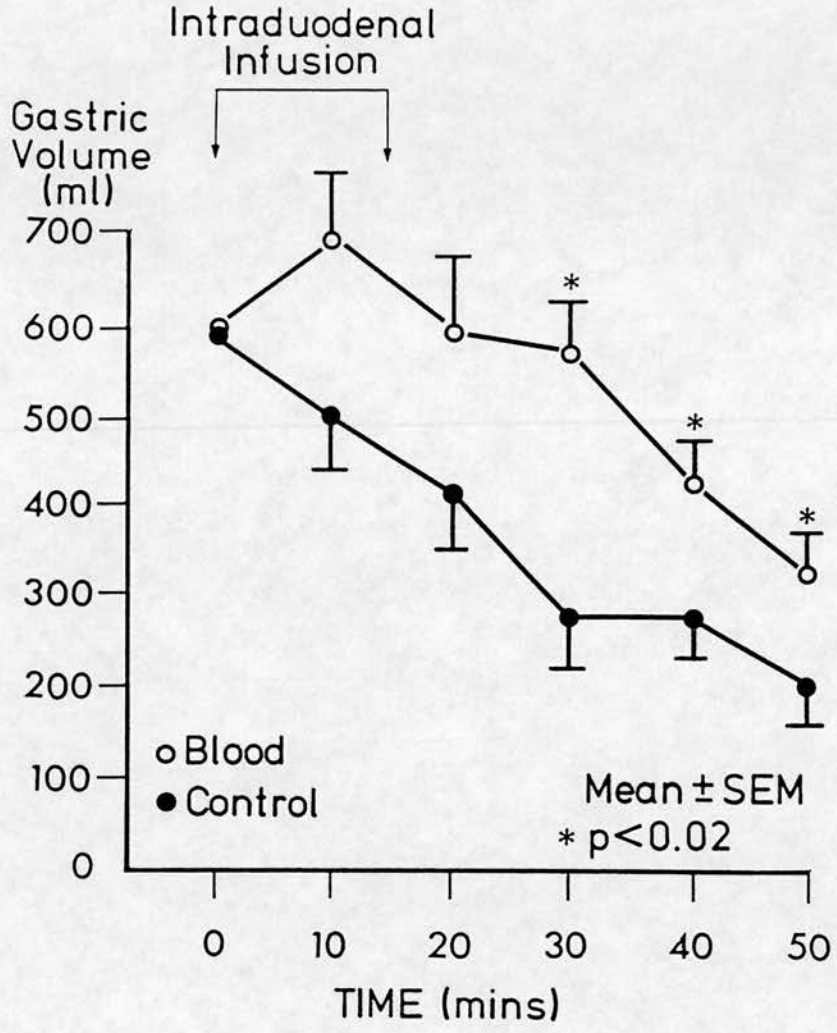


FIGURE 8

Residual gastric volumes following intraduodenal blood infusion and duodenal intubation alone in 6 healthy volunteers. Values are given and Mean ± SEM.

67.7 ± 12.7 compared with 35.5 ± 6.6 following the control study (p = NS). After egg white infusion 291 ± 36ml remained in the stomach at 50 minutes compared with 211 ± 28ml following the control study (p = NS).

GI HORMONES

GIP

Plasma GIP concentrations (ng/l) increased significantly following blood infusion compared with pre-infusion values ($p < 0.02$) (Fig. 9). Peak GIP levels were reached 21 minutes after the commencement of blood infusions being 127.9 ± 62.7 compared with the pre-infusion value of 58.3 ± 2.3 ($p < 0.02$). GIP concentrations remained significantly elevated above pre-infusion values at the end of the study 56 minutes after the start of blood infusions.

In contrast intraduodenal egg white infusion had no effect on plasma GIP concentrations at any time point studied (Fig.9).

GASTRIN

A small increase in plasma gastrin concentrations (ng/l) was noted following intraduodenal blood infusion (Fig.10) reaching peak levels of 32.1 ± 5.7 14 and 21 minutes after the start of the infusion ($p < 0.02$) compared with the pre-infusion value of 24.8 ± 5.2. Plasma gastrin remained elevated at 31.4 ± 7.1 49 minutes after the start of blood infusions ($p < 0.02$). Plasma

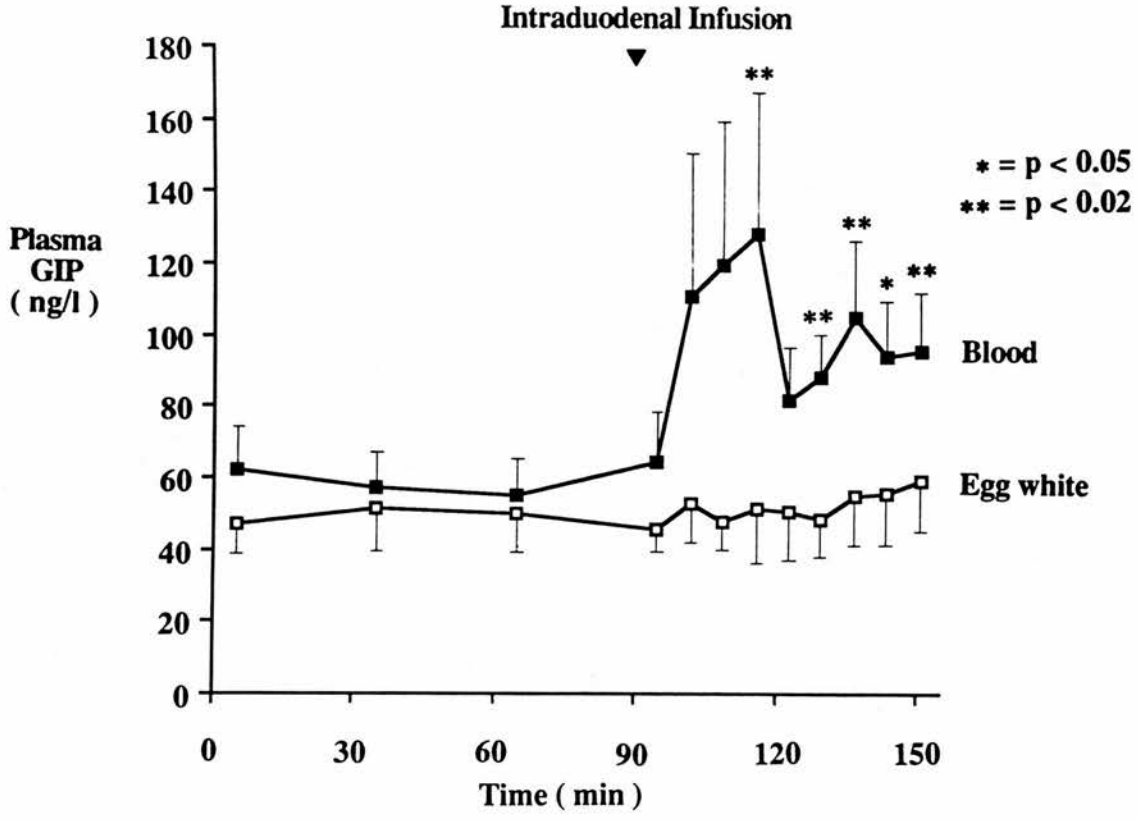


FIGURE 9

Venous plasma concentrations of GIP before and after intraduodenal infusion of blood and egg-white in 7 healthy volunteers. Values are given as Mean ± SEM.

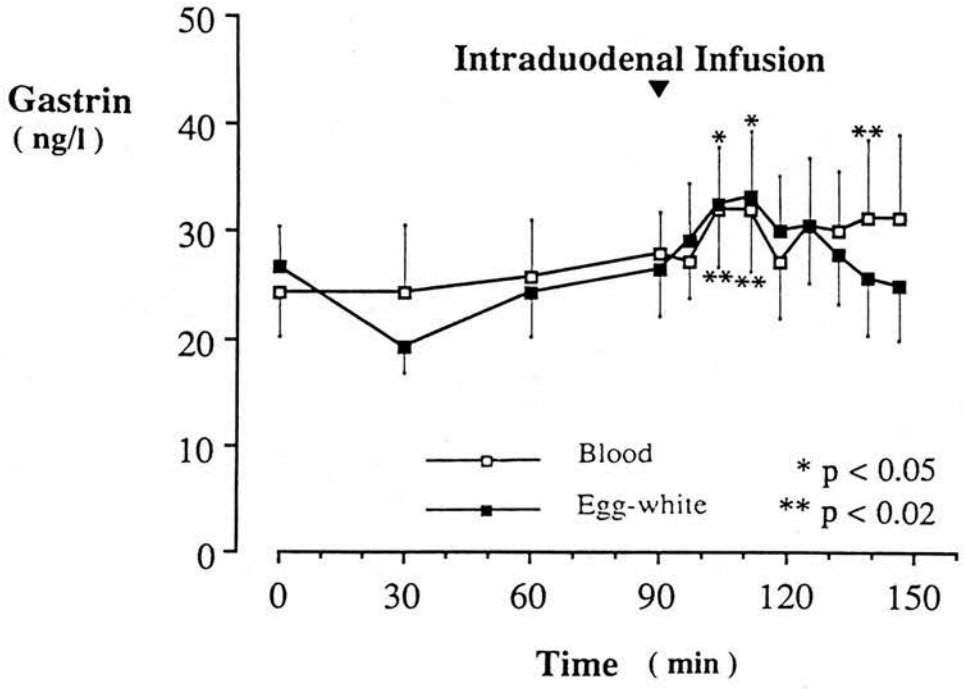


FIGURE 10

Venous plasma concentrations of Gastrin before and after intraduodenal infusion of blood and egg-white in 7 healthy volunteers. Values are given as Mean ± SEM.

gastrin concentrations (ng/l) also showed a small increase after intraduodenal egg white infusion (Fig.10) reaching peak values of 32.5 ± 5.7 and 33.3 ± 6.4, 14 and 21 minutes respectively after the start of infusions compared with the mean pre-infusion value of 25.0 ± 3.6 ($p < 0.03$).

SECRETIN

A small increase in secretin concentrations (ng/l) was seen immediately after the first intraduodenal blood infusion at 90 minutes reaching a peak level of 51.4 ± 16.9 compared with the mean pre-infusion value of 26.9 ± 4.6 ($p < 0.05$) (Fig. 11). Secretin concentrations were also significantly raised 28 and 42 minutes after blood infusion at 40.7 ± 7.8 and 34.3 ± 7.0 respectively ($p < 0.05$). Following intraduodenal egg white infusion there was also an immediate rise in plasma secretin concentrations to a peak of 51.4 ± 16.9 at 90 minutes compared with the pre-infusion value of 32.4 ± 9.4 although this failed to reach statistical significance (Fig. 11).

VIP

Intraduodenal blood infusion had no effect on plasma VIP concentrations at any time point studied (Fig. 12). Plasma VIP concentrations (ng/l) however, rose following intraduodenal egg white infusion reaching peak levels of 72.1 ± 11.8, seven minutes after the start of infusion compared with the mean pre-infusion value of 45.5 ± 6.4 ($p < 0.02$) (Fig. 12).

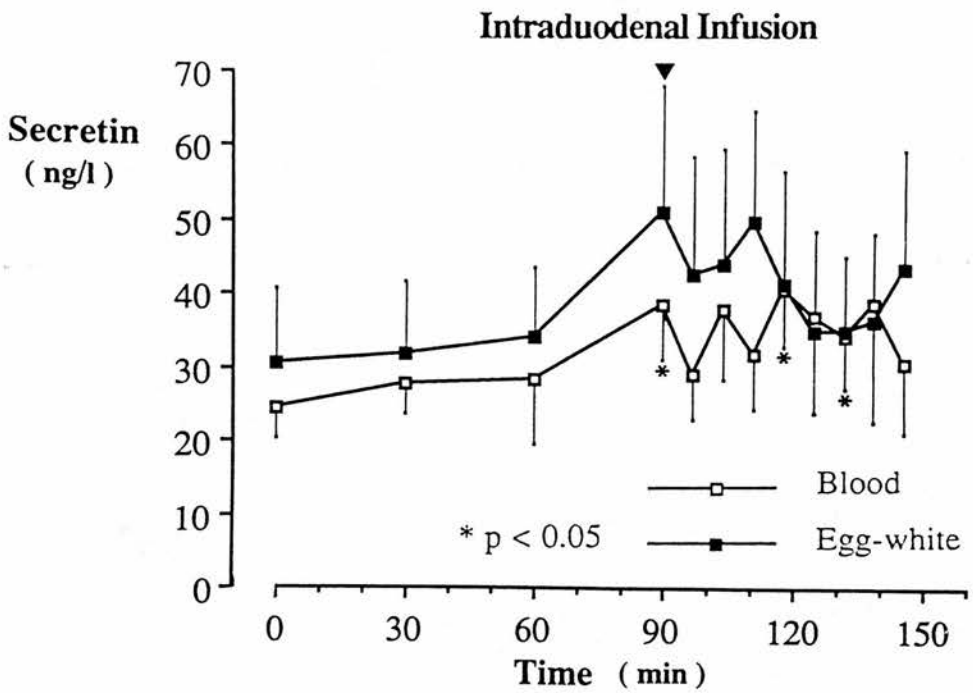


FIGURE 11

Venous plasma concentrations of Secretin before and after intraduodenal infusion of blood and egg-white in 7 healthy volunteers. Values are given as Mean ± SEM.

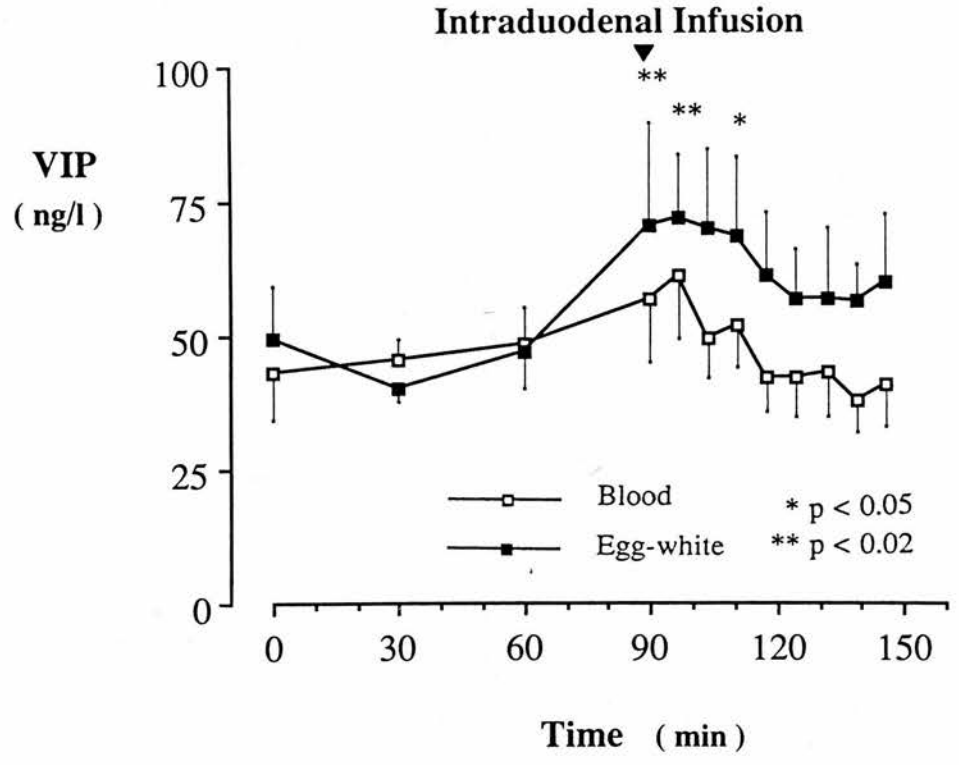


FIGURE 12

Venous plasma concentrations of VIP before and after intraduodenal infusion of blood and egg-white in 7 healthy volunteers. Values are given as Mean ± SEM.

NEUROTENSIN

Plasma neurotensin concentrations (ng/l) rose to 15.3 ± 2.3 21 minutes after intraduodenal blood infusion and reached a peak value of 17.3 ± 2.1 at 49 minutes compared with the basal value of 12.9 ± 2.6 (Fig. 13) although these just failed to reach statistical significance ($p < 0.07$). Intraduodenal egg white had no significant effect on neurotensin concentrations at any time point studied (Fig. 13).

SOMATOSTATIN

No significant changes in somatostatin concentrations were noted after either intraduodenal blood or egg white infusions (Fig. 14).

2.4 DISCUSSION

This study has demonstrated that intraduodenal blood infusion in man inhibits pentagastrin stimulated gastric acid and pepsin secretion, delays gastric emptying and increases plasma GIP concentrations. These responses may represent a locally protective physiological mechanism to facilitate haemostasis.

Gastroduodenal haemorrhage is the commonest and most clinically significant source of blood loss in patients presenting with upper GI bleeding. In a large review of 2097 patients presenting with upper GI bleeding, gastroduodenal sources of blood loss were found in 75% of cases (SILVERSTEIN et al 1981). The normal gastroduodenal

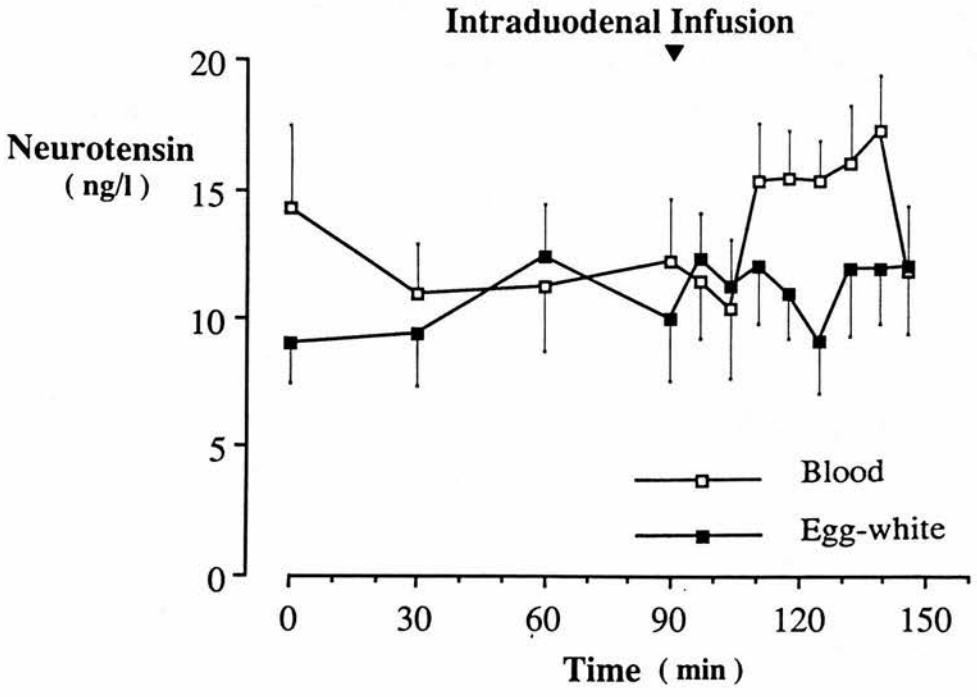


FIGURE 13

Venous plasma concentrations of Neurotensin before and after intraduodenal infusion of blood and egg-white in 7 healthy volunteers. Results are given as Mean ± SEM.

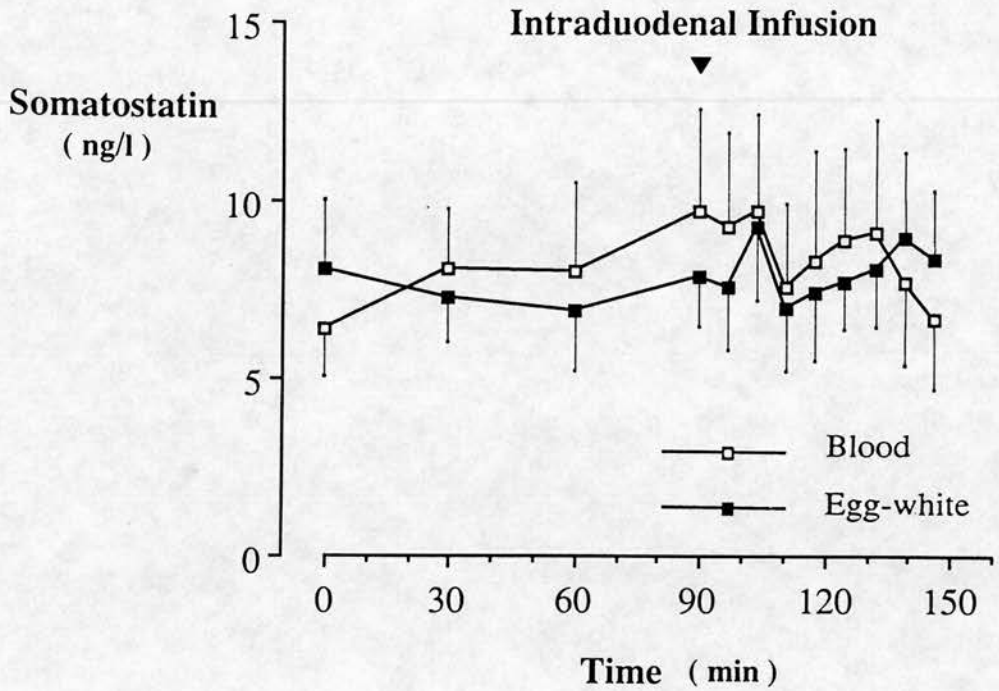


FIGURE 14

Venous plasma concentrations of Somatostatin before and after intraduodenal infusion of blood and egg-white in 7 healthy volunteers. Results are given as Mean ± SEM.

environment however, is not conducive to haemostasis. The resting pH of the stomach and proximal duodenum is usually less than 2 (RUNE 1981; HANNIBAL and RUNE 1983) and platelet aggregation and plasma coagulation are abolished at pH < 5.4 (GREEN et al 1978). Gastric juice is rich in pepsin, a potent proteolytic enzyme which digests thrombus and fibrin (LOW et al 1980; BERSTAD 1982). Furthermore, the highly vascular and motile nature of the upper GIT is likely to promote haemorrhage and inhibit haemostasis. Following simulated intraduodenal haemorrhage the three of these factors studied were all altered in a way that would facilitate haemostasis. In clinical terms the 160ml of blood infused in our study represents a very minor bleed and the changes seen may be more marked following larger bleeds where the volume of intraluminal blood is considerably greater. In addition, in clinical upper GI haemorrhage blood usually refluxes into the stomach contributing to the reduction in gastric acidity by its buffering capacity. In a single large clinical study by Chandler and Watkinson in 1953 a temporary achlorhydria was noted in patients with intraduodenal haemorrhage which was not due to blood reflux but was thought to represent a temporary inhibition of parietal cell function (CHANDLER and WATKINSON 1953).

The mechanism by which intraduodenal blood inhibits gastric secretion and motility is unclear. Intraduodenal infusions of acid (JOHNSTON and DUTHIE 1965; JOHNSTON and DUTHIE 1966), fat (SHAY et al 1939; SIRCUS 1958; WINDSOR et al 1969) or hyper/hypo- osmolar solutions (WARD et al 1969; WALLIN et al 1985) are known to inhibit acid and pepsin secretion and delay gastric emptying (ROBERTS 1931; VAN LIERE & SLEETH 1940; HUNT 1963). Although the controlling mechanisms of these responses are unknown hormonal mediation by an inhibitory 'enterogastrone' has been postulated (KOSAKA and LIM 1930; GREGORY 1967; JOHNSTON & GROSSMAN 1971). An 'enterogastrone' has therefore been defined as a substance that is released from the intestinal mucosa by contact with acid, fat or hypertonic solutions and which acts to inhibit gastric secretion and motility (GREGORY 1967). Blood has a pH of 7.35 - 7.45, is iso-osmolar and has a low fat content in the fasting state. It seems unlikely therefore that the inhibitory responses to infused intraduodenal blood seen in this study were initiated by any currently known duodenal inhibitory pathway. Moreover, intraduodenal blood being composed primarily of a protein load may be expected to stimulate gastric secretion (ISENBERG et al 1977; LANDOR and IPAPO 1977).

This study however, has provided some evidence that these secretory and motility changes following simulated intraduodenal haemorrhage may be hormonally mediated. We

have noted increases in gastric inhibitory peptide (GIP) concentrations following blood infusion alone. GIP is a polypeptide located primarily in the duodenum and jejunum (POLAK et al 1973). Its primary physiological role appears to be in the control of glucose metabolism where it acts as an insulinotropic factor (ANDERSEN et al 1978). It has known inhibitory effects on both pentagastrin stimulated gastric acid secretion and gastric motility in dogs (PEDERSON & BROWN 1972), and was originally thought to represent an enterogastrone (BROWN 1974; BROWN et al 1975). The role of GIP as an enterogastrone in man, however, is controversial. Systemic infusion of GIP in man produces inhibition of pentagastrin stimulated gastric secretion only at doses that exceed the blood concentrations seen after meals (CLEATOR and GOURLAY 1975; ARNOLD et al 1978; MAXWELL et al 1980). GIP's action as an enterogastrone, however, may either be intraluminal (UVNAS-WALLENSTEN 1980) or depend on the production of high portal concentrations which were not monitored in these studies. Although the increases in GIP concentrations seen in our study following intraduodenal blood infusion were small, these again represented systemic venous concentrations only. Intraluminal or portal venous concentrations therefore may have been more significantly elevated.

The role of other GI hormones in the mediation of these inhibitory responses is unclear, however other recently discovered inhibitory peptides such as peptide YY may be involved (GUO et al 1987). It is also possible that a combination of hormones may be responsible. A small but significant increase in secretin concentrations was seen after intraduodenal blood infusion, with a trend towards a late increase in neurotensin concentrations. Both secretin and neurotensin have known inhibitory actions on both gastric acid secretion and motility although their roles as enterogastrones remain unproven (BLACKBURN et al 1980a; VALENZUELA & DEFILIPPI 1981; SKOV OLSEN et al 1983; THOMPSON 1987). Interestingly, however, neurotensin and secretin have been shown to have a complementary inhibitory effect on gastric secretion in man which suggests that together they may function as an 'enterogastrone' (FLETCHER et al 1985).

The increase in VIP concentrations seen after intraduodenal egg-white but not blood infusion is difficult to explain. VIP is found throughout the entire length of the gut (BRYANT et al 1976) and has been shown to increase in man after intraluminal perfusion of acid, fat or ethanol but not amino acids (SCHAFFALITZKY DE MUCKADELL et al 1977). It has potent inhibitory effects on both acid and pepsin secretion (VILLAR et al 1975)

although the concentrations reached after egg-white infusion in this study may have been insufficient to induce acid inhibition.

The small increase in serum gastrin concentrations noted after both blood and egg white infusion is interesting. The proximal duodenum is a rich source of gastrin in man having an equivalent mass of stored gastrin to the gastric antrum (NILSSON et al 1973). Duodenal gastrin, however, consists mainly of G34 (BERSON & YALOW 1971; MALMSTROM et al 1976) which may represent a precursor molecule (GREGORY & TRACY 1975) and which appears to be less active than the smaller G17 which is the most common stored form in the gastric antrum (WEINER et al 1987). The duodenal release of G34 may explain the absence of acid stimulation in either of our groups following duodenal infusions.

The activating agent present in blood responsible for these inhibitory actions is unclear. The identification of the activating agent may be important, however, both to increase our knowledge of the pathophysiology of upper GI haemorrhage and perhaps to allow the development of new therapeutic regimes.

CHAPTER 3

DURATION OF GASTRIC INHIBITORY RESPONSE FOLLOWING SIMULATED INTRADUODENAL HAEMORRHAGE

3.1 INTRODUCTION

My initial study confirmed that simulated intraduodenal haemorrhage significantly inhibits pentagastrin stimulated gastric acid and pepsin secretion for at least one hour after infusion. If this apparent protective physiological mechanism is of clinical significance then a prolonged inhibitory response would be expected. In this series of experiments I have investigated the effect of simulated intraduodenal haemorrhage on acid and pepsin secretion was investigated, 3 and 12 hours following infusion to determine the duration of this inhibitory response.

3.2 EFFECT OF SIMULATED INTRADUODENAL HAEMORRHAGE ON PENTAGASTRIN-STIMULATED GASTRIC ACID SECRETION UP TO 3 HOURS POST INFUSION

3.2.1 Materials and Methods

3 healthy volunteers (2 female, 1 male), median age 29 (range 28-30) were studied after an overnight fast. The experimental study method was similar to that described in Chapter 2 for the original study. In summary, separate intraduodenal and intragastric tubes were passed under radiological control into the second part of the duodenum and body of stomach respectively. Following a 30 minute equilibration period (time 0-30 mins), each volunteer was commenced on an IV infusion of pentagastrin (0.25µg/kg/hr) to produce submaximal gastric

secretion. Gastric aspiration was then applied continuously for 60 minutes (time 30-90 mins) with 4 x 15 minute collections being analysed for volume and aliquots retained for assay. At time 90 minutes each volunteer was blindfolded and randomly received either 300ml of fresh, unclotted autologous venous blood or intraduodenal intubation alone which was chosen as a control to exclude any pentagastrin 'fade' or tachyphylaxis. On each study day 50ml of venous blood was removed from each volunteers arm every 5 minutes for 25 minutes (total volume removed = 300ml) and either directly infused into the duodenum (blood study day) or discarded (intubation alone study day). On the blood study day infusions were given as 6 x 50ml aliquots at 5 minute intervals over 30 minutes. Following the start of duodenal infusions, a further 12 x 15 minute gastric collections were taken (90-270 minutes). Volumes of each 15 minute sample were measured and aliquots retained for assay. Intraduodenal blood infusion or intubation alone were performed in random order at least one week apart. On each occasion the same volume of blood was removed.

Corrections were made for pyloroduodenal loss by infusing a non-absorbable marker, phenol red solution (1500mg/l) at 12ml/h intragastrically throughout the study (HOBSLEY & SILEN 1969). Corrections were made for duodenogastric reflux of duodenal juice by estimating

sodium concentration of the gastric aspirate (McCLOY 1978). Microscopic blood reflux was quantitated spectrophotometrically as before.

ANALYSIS

Gastric juice was analysed for H+ concentration phenol red, sodium and pepsin concentrations using the methods described in Chapter 2.

Acid output was expressed as total acid output in mmol/h for each hour before and each hour after duodenal infusions following correction for pyloroduodenal losses and duodenogastric reflux. Pepsin output was expressed as the total output in mg for each hour before and after intraduodenal infusions.

3.2.2Results

a) ACID OUTPUT

In all 3 volunteers gastric acid output decreased steadily during each of the 3 hours following intraduodenal blood infusion compared with the pre-infusion hour (Fig. 15). The acid output (mmol/h) was 35.5 ± 8.4 (mean ± SEM) in the hour preceding intraduodenal blood infusion and 25.8 ± 9.2, 24.4 ± 5.6 and 18.4 ± 7.7 one, two and three hours following blood infusion respectively. Compared with the pre-infusion hour this represented median inhibition in acid output of 33%, 28% and 41% one, two and three hours following blood

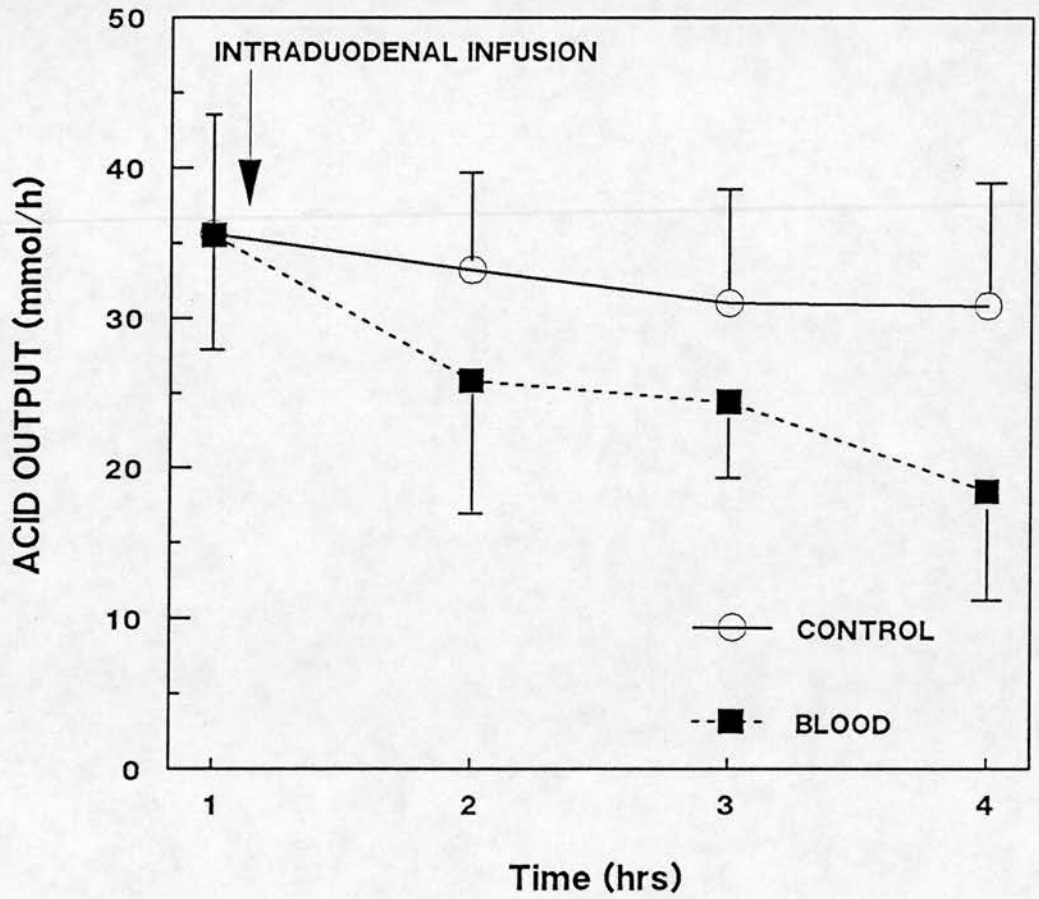


FIGURE 15

Pentagastrin-stimulated gastric acid secretion before and up to three hours following intraduodenal infusion of blood or intubation alone in 3 healthy volunteers. Results are given as Mean ± SEM.

infusion respectively. This inhibition was again accounted for by a reduction in both H+ concentration and volume of gastric juice.

In contrast with duodenal intubation alone there was little change in acid output compared with the pre-infusion hour (Fig.15). The acid output (mmol/h) in the initial hour was 35.6 ± 8.3 (mean ± SEM) compared with respective post infusion values of 33.2 ± 7.5, 31.0 ± 7.5 and 30.8 ± 8.7 one, two and three hours later. Compared with the pre-infusion hour this represented a median increase in acid output of 12% one hour later and median acid inhibition of 5% and 12% respectively, two and three hours after infusion.

No significant pentagastrin 'fade' was therefore seen up to 4 hours after commencement of pentagastrin infusions.

b) PEPSIN OUTPUT

In all 3 volunteers pepsin output decreased during each of the 3 hours following intraduodenal blood infusion compared with the pre-infusion hour (Fig. 16). Pepsin output (≡ mg sigma porcine pepsin) was 117.1 ± 16.8 (mean ± SEM) in the pre-infusion hour and 83.6 ± 2.0, 68.7 ± 7.5 and 85.6 ± 16.2 one, two and three hours after blood infusion respectively. Compared with the pre-infusion hour this represented median inhibition in pepsin output of 34%, 33% and 18% one, two and three hours after blood infusion respectively.

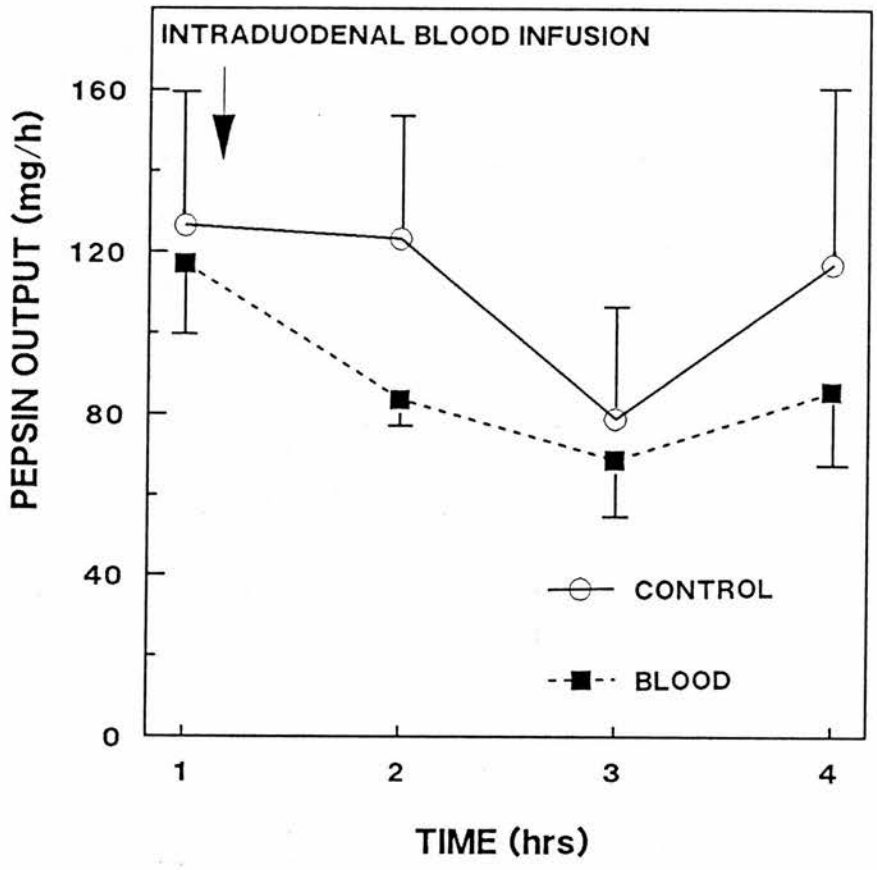


FIGURE 16

Pepsin output before and up to 3 hours after intraduodenal infusion of blood or intubation alone in 3 healthy volunteers. Results are given as Mean ± SEM.

In contrast after intraduodenal intubation alone there was little overall change in pepsin output (Fig. 16). Pepsin output was 126.5 ± 35.1 in the pre-infusion hour compared with 123.2 ± 33.5, 78.8 ± 31.3 and 117.1 ± 52.2 one, two and three hours later respectively.

3.3 EFFECT OF SIMULATED INTRADUODENAL HAEMORRHAGE AT 8PM ON OVERNIGHT GASTRIC SECRETION AND 12 HOURLY PENTAGASTRIN-STIMULATED ACID AND PEPSIN SECRETION.

In this study the effect of a simulated intraduodenal bleed at 8.00pm was examined on -

(a) overnight basal nocturnal acid and pepsin secretion

(b) pentagastrin stimulated submaximal acid secretion 12 hours later.

3.3.1 Materials and Methods

6 healthy male volunteers, median age 28 years (range 25-30) were studied in a single-blind controlled, randomised fashion.

At 8.00pm following a 6 hour fast, a size 7 Fr intraduodenal tube (Viomedex) was passed oragastrically and positioned in the second part of the duodenum. The intraduodenal position in this study was confirmed by aspiration. When two successive 5ml aspirates had pH ≥ 7 with bile staining the tube was assumed to be within the duodenum. At 8.30pm (time 0) each volunteer was blindfolded and randomised to receive either 300ml of

fresh unclotted autologous venous blood or 300ml egg-white. Egg-white having similar proportions of carbohydrate, protein and fat to blood was again chosen as the control infusion (Table 1). On each occasion 300ml of venous blood was removed as 50ml aliquots every 5 minutes for 25 minutes, on the blood study day this was infused intraduodenally, on the egg-white day it was discarded. Each infusion was given as 6 x 50ml aliquots over 5 minute intervals for 30 minutes. Intraduodenal infusions were administered in random order on separate days at least 1 week apart.

TABLE 1

COMPARATIVE CONSTITUENTS OF BLOOD AND EGG-WHITE *

	PROTEIN (g/100ml)	CHO (g/100ml)	FAT (g/100ml)	OSMOLALITY (mosmol/kg)	CALCIUM (mg/100ml)
EGG-WHITE	10.8	0.1	0	230	6
BLOOD	22.0	0.6	0.6	280	9

*Based on Diem (1962)

a) OVERNIGHT STUDY

At 9.00pm (time 30 minutes) the intraduodenal tube was withdrawn and a size 8 intragastric tube (Argyll Ltd) passed oragastrically into the body of the stomach. Five ml aspirates were withdrawn at

hourly intervals (9.00pm-8.00am) and analysed for pH and hydrogen ion concentration. pH was determined using a combined glass pH electrode (Radiometer ETS 822, Copenhagen) and titratable acidity by autotitration to pH 7 using 0.1 N sodium hydroxide (Radiometer ETS 822).

CALCULATIONS

1) Median gastric pH was calculated for each individual for the periods 10.00pm - 3.00am (termed night period), 4.00am - 8.00am (termed morning period) and 10.00pm - 8.00am (termed overnight period).

2) Median H+ concentrations were calculated for each individual for the periods 10.00am - 3.00am (night period), 4.00am - 8.00am (morning period) and 10.00pm - 8.00am (overnight period).

b) 12 HOURLY SUBMAXIMAL PENTAGASTRIN TEST

At 8.30am (time 12h) the size 8 intragastric tube was withdrawn and replaced by a size 12 vented Andersen tube (Andersen Inc, New York). Its position in the body of the stomach was confirmed by water recovery test. An IV infusion of pentagastrin (Peptavlon, ICI) 0.25µg/kg/hr was then commenced and continued throughout the study to stimulate submaximal gastric secretion. Following a 30 minute equilibration period the stomach was emptied by

aspiration and the contents discarded. Four fifteen minute collections of gastric juice were then obtained by continuous aspiration, their volumes noted and a 5ml aliquot retained for analysis. Corrections were made for pyloroduodenal loss by infusing phenol red solution (1500mg/l) as a non-absorbable marker intragastrically at 12ml/h throughout the study (HOBSLEY & SILEN 1969). Duodenogastric reflux was calculated by estimating the sodium concentration of the gastric aspirate (McCLOY 1978).

A summary of this study's protocol is shown in Figure 17.

ANALYSIS

Gastric secretion

Samples were analysed for H+, pH, pepsin and phenol red concentration as before. Acid output (mmol/h) and pepsin output (mg/h) were calculated as the total output in the hour following the start of pentagastrin infusions.

Statistical analysis

Statistical analysis was performed using the 2 sided Wilcoxon Signed Rank Sum Test for paired data. The significance level was taken at 5% ($p \leq 0.05$)

This study was approved by the local hospital Ethical Committee and written fully informed consent was obtained in each case.

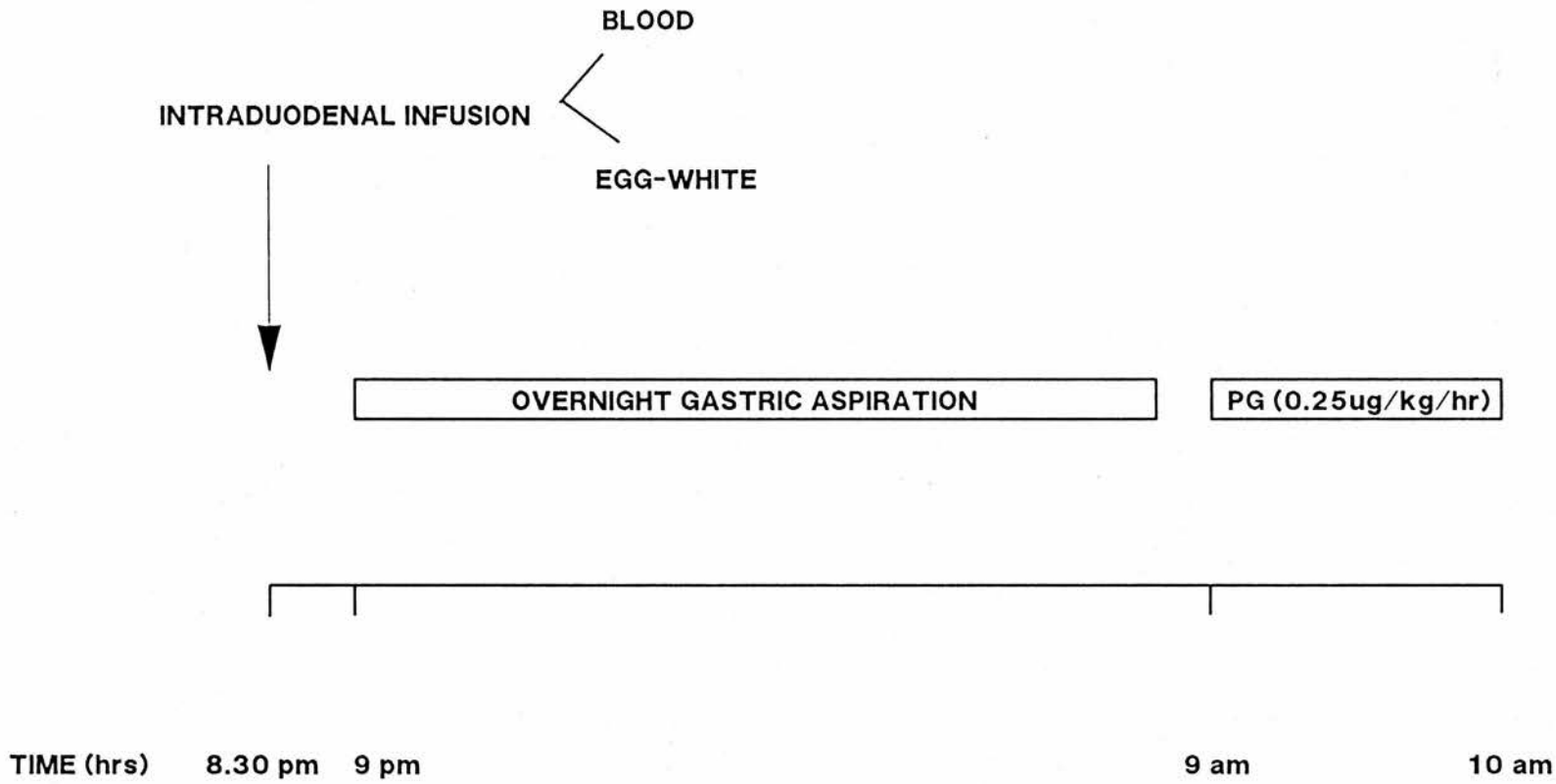


FIGURE 17 Study method for investigation of duration of inhibitory response following simulated intraduodenal haemorrhage in 6 volunteers.

3.3.2Results

a) OVERNIGHT STUDY

Median gastric pH was increased following intraduodenal blood infusion during the night period, the morning period and the total overnight period when compared to the values found during equivalent time periods after egg-white infusion (Table 2). The integrated median pH curves demonstrated the extent and duration of the intragastric pH rise after intraduodenal blood compared with egg-white infusion (Fig.18).

TABLE 2 MEDIAN INTRAGASTRIC pH VALUES FOLLOWING INTRADUODENAL BLOOD AND EGG-WHITE INFUSION

	TIME (hours)		
	NIGHT PERIOD (2200-0300)	MORNING PERIOD (0400-0800)	OVERNIGHT PERIOD (2200-0800)
BLOOD (n = 6)	3.5 (2.9-5.8)	6.2 (2.3-7.3)	4.0 (2.3-7.3)
EGG-WHITE (n = 6)	1.6 (1.4-2.2)	2.0 (1.6-4.3)	1.6 (1.4-4.3)
	$p < 0.03$	$p < 0.04$	$p < 0.03$

All values are given as medians + ranges

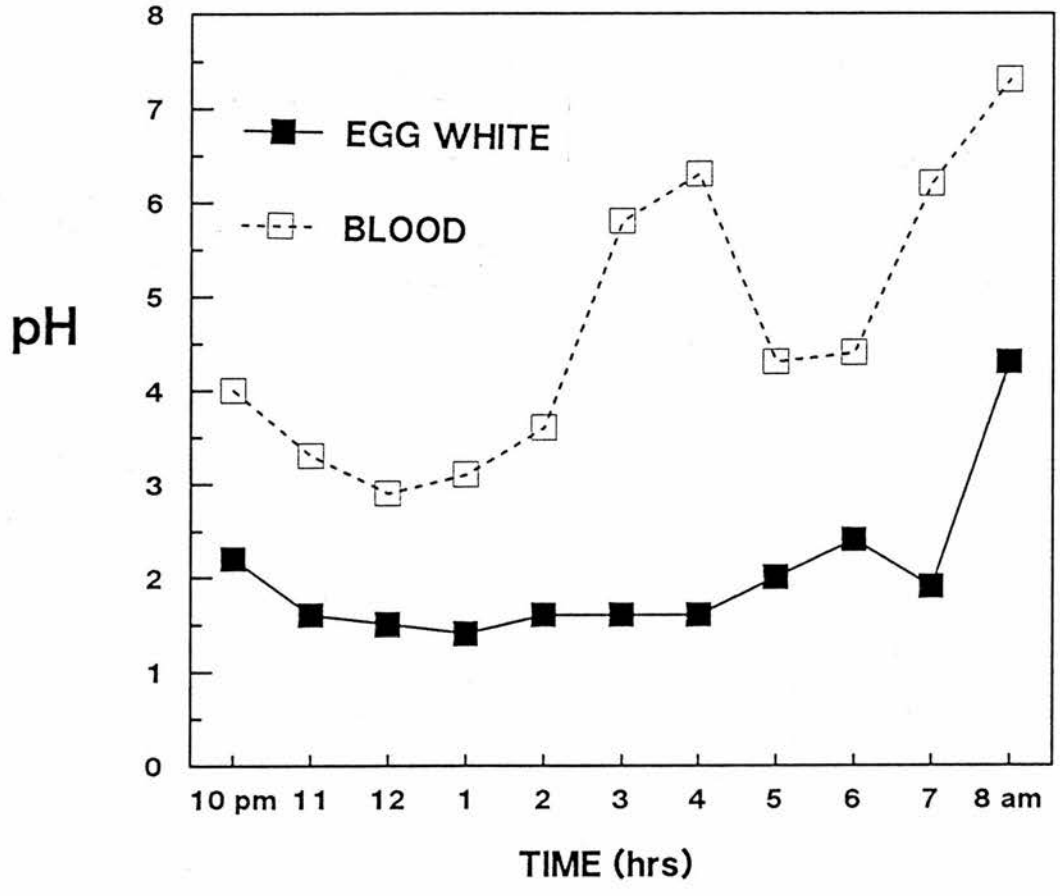


FIGURE 18

Effect of intraduodenal blood and egg-white infusion on median overnight gastric aspirate pH in 6 volunteers

Hydrogen ion concentrations of the aspirated gastric juice were lower after intraduodenal blood infusion for the night and overnight periods when compared with equivalent time periods after egg-white infusion (Table 3).

TABLE 3 MEDIAN H+ CONCENTRATIONS (mmol/l) FOLLOWING INTRADUODENAL BLOOD AND EGG-WHITE INFUSION

	TIME (hours)		
	NIGHT PERIOD (2200-0300)	MORNING PERIOD (0400-0800)	OVERNIGHT PERIOD (2200-0800)
BLOOD (n = 6)	40.3 (19-49)	20.8 (2-28)	28.3 (2-49)
EGG-WHITE (n = 6)	45.8 (38-57)	23.7 (15-42)	39.8 (15-57)
	$p < 0.05$	NS	$p < 0.02$

b) 12 HOURLY SUBMAXIMAL PENTAGASTRIN TEST

Gastric acid output decreased in each of the six volunteers 12 hours after the last intraduodenal blood infusion when compared to the acid output 12 hours after egg-white infusion (Fig.19). Mean acid

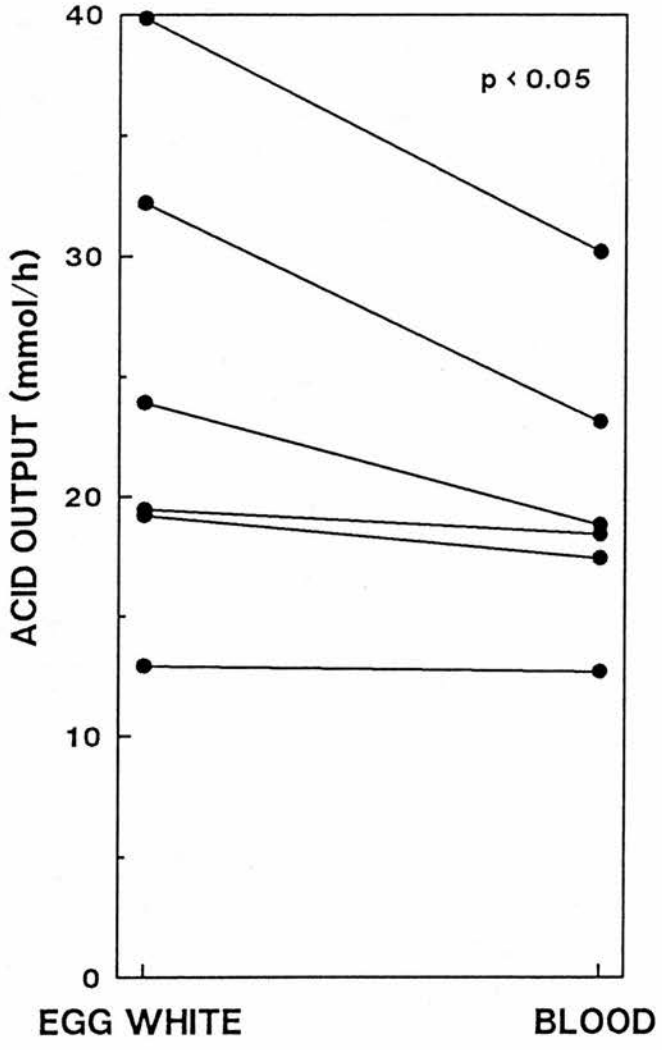


FIGURE 19

Submaximal pentagastrin-stimulated acid secretion 12 hours after intraduodenal blood and egg-white infusion in 6 healthy volunteers.

output (mmol/h) was 19.7 ± 2.4 (mean ± SEM) 12 hours after blood infusion and 23.7 ± 3.8 after egg-white infusion ($p < 0.05$). This represented a mean inhibition in acid output of 14% 12 hours after intraduodenal blood infusion compared with acid outputs found after egg-white infusion.

Pepsin output (≡ mg sigma porcine pepsin) was also decreased 12 hours after intraduodenal blood infusion when compared to the output 12 hours after egg-white infusion (Table 4). Mean pepsin output was 57.4 ± 15.9 (mean ± SEM) 12 hours after intraduodenal blood infusion and 91.2 ± 14.0 after egg-white infusion ($p < 0.05$). This represented a median reduction in pepsin output of 37% 12 hours after intraduodenal blood infusion compared with the pepsin output found after egg-white infusion. The inhibition of pepsin output seen after blood infusion was again accounted for by a reduction in both volume and concentration of pepsin secretion.

TABLE 4 PEPSIN OUTPUT (mg/h) IN 6 VOLUNTEERS 12 HOURS AFTER INTRADUODENAL BLOOD AND EGG-WHITE INFUSION

VOLUNTEER	EGG-WHITE	BLOOD
A	59.7	7.4
B	70.7	37.3
C	151.0	116.0
D	70.7	51.2
E	83.9	89.3
F	111.3	43.3
Mean	91.2	57.4
SEM	14.0	15.9

$p < 0.05$

3.4. DISCUSSION

These studies have shown that intraduodenal blood infusion inhibits pentagastrin stimulated acid and pepsin secretion progressively up to 3 hours following infusion and this inhibition, although less marked, is still present 12 hours later. In addition, intraduodenal blood infusion at 8.00pm increases overnight (10.00pm-8.00am) intragastric pH suggesting continued inhibition of basal secretion over this period.

Although the inhibition of gastric acid and pepsin secretion demonstrated in my initial study following simulated intraduodenal haemorrhage may indicate a locally protective physiological mechanism any benefit in clinical upper GI bleeding will depend on both the magnitude and duration of the inhibitory response. This study has shown a progressive inhibition of pentagastrin-stimulated acid secretion up to 41% 3 hours following blood infusion compared with pre-infusion values. The volume of infused blood used in this study to simulate intraduodenal haemorrhage still represents a small volume in terms of clinically significant upper GI bleeding. It is possible therefore the changes may be even more marked following larger bleeds. In addition, the absence of any decline in pentagastrin-stimulated gastric secretion over the four hours of infusion in the control study adds further evidence to the lack of demonstrable pentagastrin fade in human studies (CHIN et al 1986).

Although the exact duration of these acid inhibitory responses to simulated intraduodenal haemorrhage has not been clearly defined, the effect appears to persist for at least twelve hours with a maximum response reached between three to twelve hours after the 'bleed'. Continuing acid and pepsin inhibition for such a period of time may increase intragastric pH allowing coagulation to return to normal with stabilisation of platelet aggregates and

thrombus formation. Clot stabilisation by fibrin deposition may then provide a protective haemostatic plug thereby reducing the risk of rebleeding.

The prolonged duration of this acid inhibitory response up to 12 hours following blood infusion is interesting. Such inhibition of gastric acid secretion is unlikely to be neurally mediated and if hormonally mediated suggests that either the circulating hormone has a prolonged duration of action or that the hormone release continues long after blood loss into the gut. GIP, a possible mediator of these responses discussed in Chapter 2, has a relatively long half life, around 20 minutes, with a low metabolic clearance rate of 2.6mh/kg (KHALIL et al 1987). Neurotensin, another 'candidate' hormone has a shorter half life of 3.8min (BLACKBURN et al 1980b) although being a terminal ileal gut peptide is released much later than GIP after duodenal instillation. There is now also increasing evidence that colonic release of inhibitory peptides may be important in control of gastric secretion (SOON-SHIONG et al 1980; LLUIS & THOMPSON 1988). It is interesting to speculate that in GI bleeding luminal blood traversing the GI tract may sequentially activate inhibitory GI hormones resulting in prolonged gastric secretory inhibition.

In conclusion, this study has added further evidence that intraduodenal blood infusion inhibits gastric acid and pepsin secretion, the process appears progressive up

to 3 hours following infusion and persists up to 12 hours later. These inhibitory effects may have important clinical relevance in initiating a prolonged locally protective physiological response in upper GI bleeding.

CHAPTER 4

EFFECT OF SIMULATED INTRADUODENAL HAEMORRHAGE ON BLOOD COAGULATION

4.1. INTRODUCTION

My initial study showed a significant reduction in gastric acid and pepsin secretion and gastric motility following simulated intraduodenal haemorrhage which may represent a protective physiological response to promote haemostasis. A recent study by Blair has suggested that upper GI bleeding may induce a hypercoagulable state which may also act in a protective manner to facilitate haemostasis (BLAIR et al 1987). It is not clear however whether this hypercoagulable response simply reflected a systemic response to haemorrhage or whether the effect was unique to GI bleeding suggesting a luminally activated mechanism.

This study was therefore performed to examine the effects of simulated intraduodenal haemorrhage on blood coagulation parameters in healthy volunteers.

4.2 MATERIALS AND METHODS

Seven healthy volunteers (6 female, 1 male) with a median age of 29 years (range 25-36) were studied in a single blind controlled fashion.

The experimental design was identical to my original method as described in Chapter 2. In summary, a size 8 duodenal tube (Viomedex Ltd) was passed under fluoroscopic control into the second part of the duodenum allowing infusion of either 160ml autologous venous blood or 160ml egg-white (similar protein and carbohydrate content to

blood). Each infusion was given as 4 x 40ml aliquots over 5 minute intervals in randomised order at least 1 week apart. On each occasion the same volume of blood was removed (160ml). Ten ml aliquots of venous blood were collected for coagulation studies at time 0 min, immediately prior to intraduodenal infusion at 90 min and one hour following the start of infusions at 150 mins. At each time period the following were measured.

1) prothrombin time
2) partial thromboplastin time
3) thrombin time.

Statistical Analysis

Paired samples for each individual were compared for equivalent time periods after intraduodenal blood and egg-white infusion using the Wilcoxon Signed Rank Sum test (2 sided). Significance was taken as $p \leq 0.05$.

4.3. RESULTS

The prothrombin time (PT) was similar on each study day before intraduodenal infusions at 0 and 90 mins (Table 5). Sixty minutes following intraduodenal infusions at time 150 mins the PT (mean ± sem) was 15.0 ± 0.5 (seconds) following blood infusion and 14.9 ± 0.3 following egg-white infusion (p = NS).

TABLE 5 **PROTHROMBIN TIME (secs)**

	TIME (min)		
	0	90	150
BLOOD(n=7)	14.7 ± 0.5	15.0 ± 0.5	15.0 ± 0.5
EGG WHITE (n=7)	14.9 ± 0.5	14.9 ± 0.3	14.9 ± 0.3

Mean ± SEM

Partial thromboplastin time (PTT) was also similar before intraduodenal infusions on each study day at 0 and 90 minutes (Table 6). Sixty minutes following intraduodenal infusions at time 150 mins, the PTT (seconds) was 45.5 ± 2.4 after blood infusion and was similar at 39.3 ± 1.0 (mean ± sem) following egg-white infusion (p = NS).

TABLE 6 **PARTIAL THROMBOPLASTIN TIME (secs)**

	TIME (min)		
	0	90	150
BLOOD (n=7)	45.4 ± 1.3	42.6 ± 1.7	45.5 ± 2.4
EGG WHITE (n=7)	43.0 ± 1.7	41.3 ± 1.7	39.3 ± 1.0

Mean ± SEM

Thrombin time (TT) was similar before intraduodenal infusions in both study groups at 0 and 90 mins (Table 7). Sixty minutes after intraduodenal infusions at 150 min TT (seconds) was 9.3 ± 0.3 (mean ± sem) following blood infusion and 9.3 ± 0.6 after egg-white infusion (p = NS).

TABLE 7 **THROMBIN TIME (secs)**

	TIME (min)		
	0	90	150
BLOOD (n=7)	9.3 ± 0.2	9.3 ± 0.4	9.3 ± 0.3
EGG WHITE (n=7)	8.9 ± 0.4	9.1 ± 0.5	9.3 ± 0.6

Mean ± SEM

4.4. DISCUSSION

This study has demonstrated that simulated intraduodenal haemorrhage has no effect on blood coagulation as measured by the prothrombin time, partial thromboplastin time or thrombin time. This preliminary study suggests the hypercoagulation demonstrated by Blair et al following upper GI haemorrhage may represent a general response to haemorrhage rather than a specific GI mediated event.

There are certain important limitations however in attempting to devise an experimental model of upper GI haemorrhage in healthy volunteers to investigate changes in coagulation parameters. Firstly, when considering a possible GI mediated response, the volume of intraduodenal blood infusion may be important. In this study we examined the effect of only 160ml of intraduodenal blood infusion on coagulation parameters. Considerably larger volumes of blood are lost into the gut lumen in clinical upper GI haemorrhage, therefore GI mediated changes in systemic blood coagulation may still occur with larger volumes of blood loss. Secondly, the time period following GI haemorrhage may be important when considering a hypercoagulable response. Blair et al examined coagulation parameters within 24 hours of presentation with upper GI bleeding. In this study, blood coagulation was examined only one hour following blood infusion. It is therefore possible that coagulation changes may require a longer period to develop.

Although the parameters of blood coagulation measured in this study did not change after simulated duodenal haemorrhage, it is possible that more sensitive indicators of hypercoagulation may have detected alterations.

In conclusion, intraduodenal infusion of blood produced no alterations in blood coagulation as measured by PT, PTT and TT in seven healthy volunteers.

CHAPTER 5

IN-VITRO STUDIES OF THE BUFFERING EFFECTS OF BLOOD AND GASTRIC JUICE

5.1 INTRODUCTION

One of the initial lines of defence against continuing intragastric haemorrhage may be the endogenous buffer system present in the stomach. Intraluminal blood itself is probably one of the most important early buffers providing a more physiological pH locally at the bleeding site allowing haemostasis to occur. As blood coagulation is particularly sensitive to alterations in pH, being abolished at pH < 5.4 (GREEN et al 1978) it is important to confirm the exact buffering capabilities of blood in gastric juice. A series of in-vitro experiments was therefore designed to determine the buffering capacity of blood in gastric juice.

5.2 METHODS

Gastric juice was collected and pooled from duodenal ulcer patients undergoing pentagastrin stimulated (Peptavlon, ICI 6μg/kg) acid secretory studies. A 5ml aliquot of this fresh gastric juice was then taken for estimation of pH (Radiometer Glass Electrode ETS 822, Radiometer, Copenhagen) and hydrogen ion activity by titration to pH 7 with 0.1M sodium hydroxide using an autotitrator (Radiometer ETS 822). Further 5 ml aliquots of this gastric juice were then removed, added to a glass beaker and maintained at 37 degrees Centigrade. To each 5ml gastric juice sample was then added increasing volumes of fresh unclotted human venous blood from 0ml up to 10ml

in 0.5ml increments. Each sample was stirred and the final volume kept constant at 15ml by the addition of distilled water. A 5ml aliquot of each sample was then taken after mixing for estimation of pH and hydrogen ion activity. Ten studies were performed on separate days with pentagastrin-stimulated gastric juice of varying pH and hydrogen ion activity from duodenal ulcer subjects. All venous blood samples were taken from healthy volunteers and were of equivalent haemoglobin concentration and pH.

As a control experiment the buffering effect of raw egg-white (which has approximately similar protein and carbohydrate content to blood) on gastric juice was studied in identical fashion in 9 separate studies. The egg-white used was obtained from a similar batch of eggs from a single chicken strain. Egg-white protein does not differ widely between identical strain chickens (PARKINSON 1966).

Analysis

Results were expressed as pH and hydrogen ion concentration. For each sample the added blood or egg-white volume was expressed as a percentage of the gastric juice volume (total = 5ml) and called % blood or % egg-white volume respectively.

Comparisons between blood and egg-white groups were made using the unpaired Student's T test. Significance was taken at the 5% level ($p \leq 0.05$)

5.3 RESULTS

The addition of increasing volumes of venous blood to a fixed volume of gastric juice increased the pH progressively (Fig.20). After 4mls of blood the median pH of the blood/gastric juice mixture was increased from 1.9 to 5.9 (range 4.4-6.2). The addition of further volumes of blood however, had only a minor effect on the pH of the gastric juice with a median pH of 6.3 (range 5.9-6.7) being reached after 10mls blood. The combination of increasing volumes of egg-white with gastric juice resulted in a slower rise in pH compared with the blood:gastric juice mixture (Fig. 20). This resulted in a significant decrease in the buffering capacity of egg-white compared with blood after the addition of 1, 1.5, 2.0 and 2.5mls of their respective solutions to the fixed volume of gastric juice (Fig. 20).

The addition of increasing volumes of either blood or egg-white had no significant effect on the titratable acidity of gastric juice (Fig.21).

5.4 DISCUSSION

These results have shown that blood may act as an endogenous buffer in the presence of gastric juice however a near equivalent volume of blood:gastric juice was required to raise the pH well above 5.4 where coagulation could be initiated. In addition, the

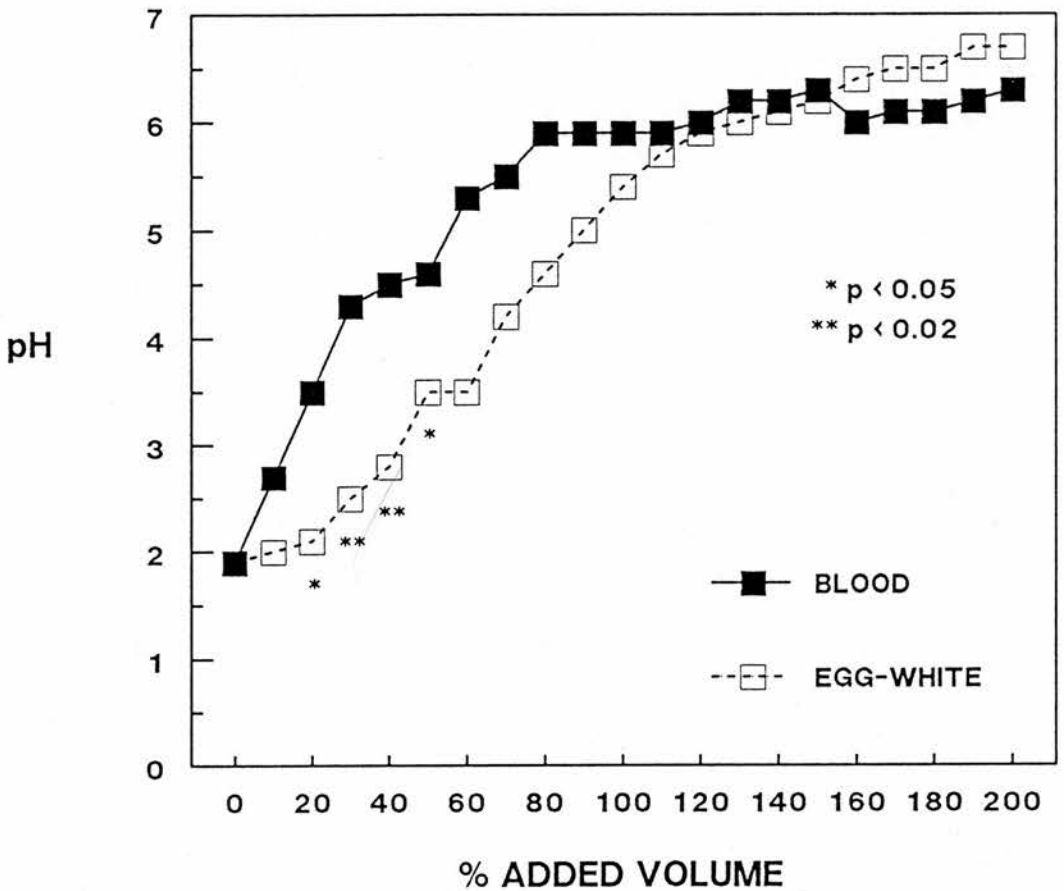


FIGURE 20

The buffering effects of increasing volumes of blood and egg-white on median pH of gastric juice.

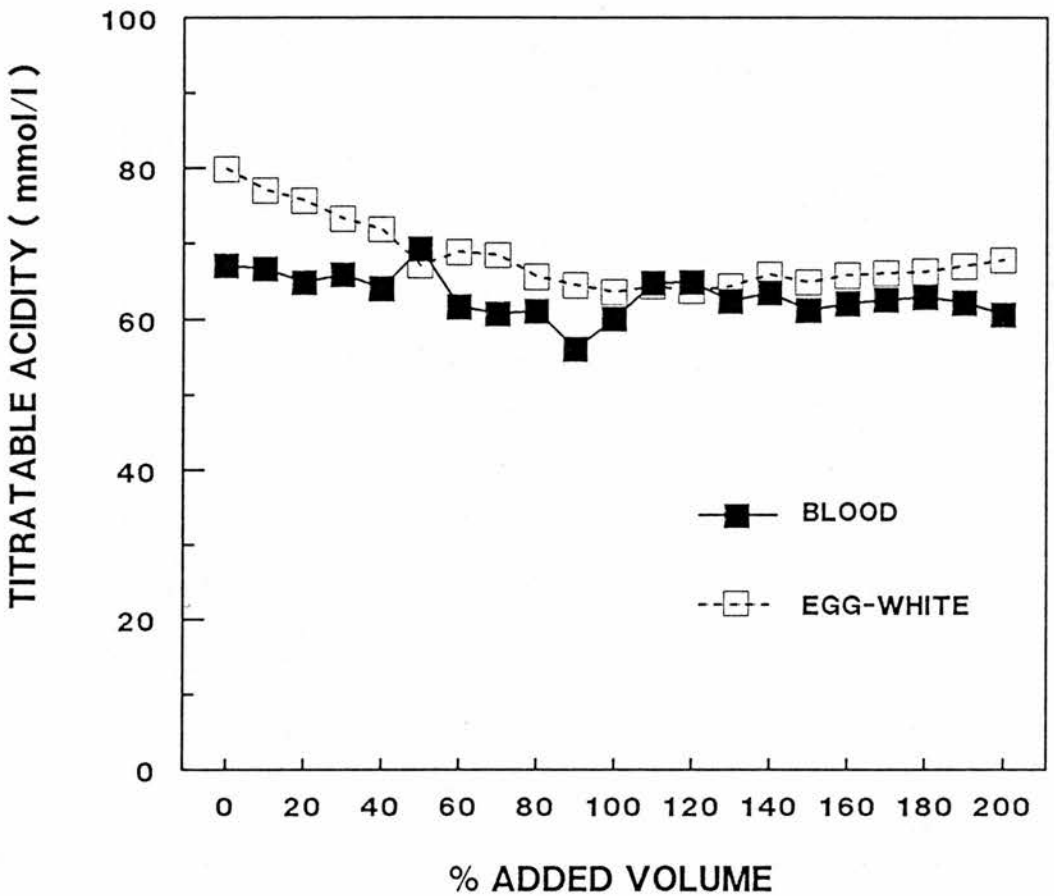


FIGURE 21

The effect of increasing volumes of blood or egg-white on the titratable acidity of gastric juice. Values are given as Means.

buffering capacity of blood was slightly greater than that of egg-white which was used as control having a similar protein content.

The titratable acidity of gastric juice being the sum of free hydrogen ion concentration and unionised hydrogen concentration as expected did not show any marked change following the addition of either buffering agent (BARON 1978).

There are several endogenous buffering systems present in the upper GI tract which may be activated during haemorrhage. Firstly intraluminal blood which acts locally both at the mucosal bleeding site and throughout the stomach; secondly,the non-parietal alkaline component of gastric juice (HOLLANDER 1952); thirdly, gastric mucus which, being a glycoprotein, may buffer acid and protect against peptic erosion (BODI et al 1956) and whose production may be stimulated by contact with gastric acid (HENNING 1949; JANOWITZ & HOLLANDER 1954); and fourthly, tissue proteins exposed by a mucosal breach may also add to the local buffering capacity. Intragastric blood is probably the most important early buffering system providing initial protection against continuing acid/pepsin attack. These studies have shown however that the relative volumes of blood:gastric juice are important in determining the overall buffered pH with a ratio of >1 being required to raise the combined pH above 6.0 where coagulation may

proceed. In the clinical situation upper GI bleeding may occur in both the fasting and stimulated stomach where gastric juice volumes vary considerably. It seems likely therefore that this buffering capability of intragastric blood represents only a transient defence mechanism allowing initial haemostasis to occur prior to possibly more effective protective mechanisms.

The important buffering agents in blood are bicarbonate, haemoglobin, plasma proteins and phosphates (BAGGOT 1982). Intracellular proteins, phosphate and other inorganic compounds are also important buffers which may be released by cell lysis on contact with gastric juice. Deoxygenated haemoglobin is a weaker acid in the reduced form and therefore venous blood is a slightly better buffer than arterial blood (LINTON 1984). Peptic ulcer bleeding is usually arterial in nature and therefore its intrinsic buffering capacity may be slightly poorer than shown in these in vitro studies. Although there are high concentrations of these buffers in blood, the buffering power of a system depends not only on the buffer's concentration but also on the pH at which it is working (GANONG 1977). Intragastric pH lies normally between 1-2 (McLAUCHLAN et al 1988), well below the optimum working pH of the blood's buffers. The pK of venous blood which is equivalent to the optimum pH for each of these buffers lies between 6.2 - 7.4 (BAGGOT 1982). Egg-white consists essentially of an aqueous

solution of proteins - ovalbumin, conalbumin and ovomucoid, which are all glycoproteins and have a similar pK (PARKINSON 1966).

From these in-vitro experiments despite the low pH in the stomach, intragastric blood should act, at least initially, as a buffer raising the local mucosal pH and allowing coagulation to occur. As bleeding stops however local buffering power is diminished, with continuing acid/peptic activity local mucosal pH may again fall, coagulation is disrupted and rebleeding may occur. Clearly these endogenous buffering systems are not the only line of defence as this cycle of bleeding/cessation of bleeding occurs in only a small percentage of patients. It may be that the presence of intragastric blood as in the intraduodenal bleeding studies also initiates protective effects on acid/pepsin secretion and/or gastric motility which may facilitate haemostasis.

In conclusion blood acts as a buffering agent in gastric juice, but requires an equivalent volume of blood:gastric juice to raise the pH above 5.4 where coagulation may be initiated. This may represent the first line of defence against continuing acid/pepsin attack and haemorrhage, however it is likely that other protective mechanisms exist to reinforce and prolong this haemostasis.

CHAPTER 6

EFFECT OF SIMULATED INTRAGASTRIC HAEMORRHAGE ON GASTRIC ACID SECRETION, GASTRIC MOTILITY AND GASTROINTESTINAL HORMONES

6.1 INTRODUCTION

Initial experimental studies in normal volunteers have demonstrated that simulated duodenal haemorrhage inhibits acid and pepsin secretion and delays gastric emptying, responses which may facilitate haemostasis in the adverse environment of the upper GI tract. It is common in upper GI bleeding however, for blood to be found in the stomach either indirectly from an oesophageal or duodenal source, or directly from a gastric lesion. Intragastric blood constitutes a concentrated protein meal which would be expected to stimulate gastric secretion by both neural and hormonal mechanisms (BEAUMONT 1833; WOODWARD et al 1954; GROSSMAN 1967) and possibly overcome any protective responses induced by duodenal blood. It is important therefore to establish the effects of intragastric blood on gastric secretory and motility parameters to determine whether similar protective responses occur. The aim of this study was therefore to determine the effects of simulated intragastric haemorrhage on gastric acid secretion, gastric emptying and serum gastrin.

6.2 MATERIALS AND METHODS

Gastric Secretion and Motility Study

The effect of simulated intragastric haemorrhage on acid secretion and motility was studied in six healthy male volunteers (median age 29 years, range 28-36).

Following an overnight (12 hrs) fast a size 10 vented nasogastric tube (Andersen Inc, New York) was passed perorally into the body of the stomach and its position confirmed by water recovery test (HASSAN and HOBSLEY 1970). At time -30min continuous nasogastric suction was commenced and two basal gastric collections were taken at 15 min intervals, the volume of each noted and a 5ml aliquot retained for analysis. At time -10min each volunteer was blindfolded and 160ml venous blood removed in 4 x 40ml heparinised syringes (250u sodium heparin/40ml syringe) at 2 minute intervals. Volunteers were then randomised to receive intragastrically either 160ml of autologous heparinised venous blood or 160ml egg-white acting as control having similar nutrient content pH and osmolarity (ROMANOFF and ROMANOFF 1949). At time 0 mins the blood or egg-white were delivered intragastrically as 4x40ml aliquots at 1min intervals, each aliquot having 5ml 14C-polyethylene glycol (PEG) (Amersham International) added acting as a non-absorbable marker. A 5ml aliquot of this test meal mixture was retained for 14C-PEG assay. The total dose of 14C-PEG infused into the stomach was equivalent to 0.9MBq. Immediately after the last aliquot of blood or egg-white was given the intragastric contents were mixed and a 10ml aliquot retained for analysis. The gastric contents continued to be mixed at regular intervals and a further 10ml aliquot was removed at 10min for analysis. At 20min the stomach was emptied

completely, the volume noted and a 10ml aliquot retained for analysis. After this, the stomach was then lavaged with 100ml distilled water, the residual volume recorded (wash volume) and a 10ml sample retained for analysis. Each subject underwent an identical study with the alternate intragastric infusate at least 1 week later. On each occasion the same volume of blood was removed, on egg-white infusion days this was discarded.

Gastrin Studies

Serial blood samples were taken before and after intragastric infusions to investigate changes in gastrin secretion. Three 10ml samples of venous blood were removed at 15min intervals during the basal collection period and added to heparinised tubes at times -30, -15, and 0 minutes. After intragastric infusions further venous blood samples were taken at 15min intervals until time 60min with the final sample taken 90min after the start of the infusions. All heparinised venous blood samples were immediately centrifuged, the plasma removed and stored at -20 degrees Centigrade for later assay.

ANALYSIS

Gastric Secretion

Gastric juice was analysed for:

1. Hydrogen ion concentration by automatic titration to pH 7.0 with 100mmol/l sodium hydroxide using an Autotitrator (Radiometer, ETS 822, Copenhagen).
2. 14C-PEG radioassay was measured by liquid scintillation counting (Packard Tri-Carb 300, Canberra Packard, Berks). Aliquots (0.2ml) of each gastric sample were initially added to a solubiliser solution Soluene 350 (Canberra Packard) and 150-propyl alcohol in a 1:2 volume ratio. After overnight incubation to allow complete solubilisation, 0.5ml hydrogen peroxide solution was added and samples incubated at 40 degrees Centigrade for a further 30 minutes. At this stage, 10ml Hionic Fluor Scintillator (Canberra Packard) was then added and counted for 10 minutes under 14C conditions with an inbuilt quench correction.

Gastrin

The gastrin assay was performed by radioimmunoassay (appendix) using antibody R98 which has a lower limit of detection of 5ng/1 (ARDILL 1973). The gastrin estimations were all performed in a single batch.

CALCULATIONS

Gastric secretion and motility

a) Basal acid output (mmol/h) was calculated by summing the outputs during the two 15 minute basal collection periods and multiplying by two.

b) To calculate net gastric secretion and transpyloric loss of gastric contents the method of Hunt (1951) was employed. The following symbols have been used:

V1 = volume of test meal instilled

V2 = volume aspirated after 20 min

V3 = wash volume

Vp = volume discharged through the pylorus in 20min

Vs = volume secreted in 20min (this represents the resultant of the volume of gastric secretions plus the volume of contaminant secretions i.e. saliva, duodeno-gastric reflux, minus the volume of water absorbed from the stomach)

PEG1 = PEG concentration in test meal

PEG2 = PEG concentration in aspirate at 10min

PEG3 = PEG concentration in aspirate at 20min

PEG4 = PEG concentration in wash

C1 = H+ concentration in test meal

C2 = H+ concentration in aspirate at 10min

C3 = H+ concentration at 20min

The following equations were then used to calculate net fluxes and volume changes.

1) Residual Volume (Vr) = V3 (PEG4/PEG3)

2) Corrected volume recovered from stomach (Vc) = V2 + Vr

3) Vp = (V1 PEG1 - Vc PEG3)/PEG2

4) Vs = Vc + Vp - V1

5) Net secretion of H+ = (Vc. C3 + Vp. C2 - V1. C1)

A positive net flux denotes secretion into the gastric lumen. The delivery of acid into the duodenum (Hp) was calculated as follows:

Hp = Vp (H1 + H2)/2

where H1 = acid concentration in the instillate and H2 = acid concentration in the aspirate.

Gastrin

Fasting gastrin values were expressed as the mean of the 3 pre-infusion samples at -30, -15 and 0 minutes. The integrated response to intragastric blood and egg-white was calculated for each individual by estimating the area under the plasma gastrin/time curve using the trapezoid method (YEH and KWAN 1978).

Statistical Analysis

Results are given as mean ± standard error of the mean (SEM). Statistical analysis was performed using the paired Wilcoxon Signed Rank Test (2 sided). Results were considered significant when $p \leq 0.05$.

Written, fully informed consent was obtained in each case and the study was approved by the local hospital Ethical Committee.

6.3 RESULTS

Gastric Secretion

a) Basal Secretion:

The mean basal acid output (mmol/hr) prior to infusions was 5.9 ± 2.6 on the blood infusion day and 4.7 ± 1.9 on the egg-white infusion day (p = NS).

b) Acid concentration:

The concentration of acid (mmol/l) aspirated from the stomach after 20 minutes was 40.4 ± 9.9 (mean ± SEM) after egg-white infusion and 16.6 ± 7.2 after blood infusion ($p < 0.05$) (Table 8).

c) Volume secreted (Vs):

There was an increase in secretion rates (ml/20min) following intragastric egg-white infusion being 198.2 ± 68.6 compared with 36.1 ± 13.3 after intragastric blood infusion ($p < 0.05$) (Table 9).

d) Net acid secretion:

There was a positive net flux of acid (net secretion of acid) in all six volunteers following both egg-white and blood infusion. Net acid secretion (mmol/20min) however, was less following intragastric blood infusion being 2.3 ± 1.3 compared with 5.6 ± 3.1 after egg-white infusion ($p < 0.05$) (Table 8).

e) Acid delivery into the duodenum (Hp):

The acid load (mmol/20min) delivered into the duodenum was less following intragastric blood infusion being 1.1 ± 0.6 compared with 7.2 ± 2.6 after egg-white infusion ($p < 0.03$) (Table 8).

Gastric Emptying

a) Corrected residual volume (Vc):

The corrected residual gastric volume (ml) at 20min was 57.4 ± 10.3 following intragastric egg-white infusion and 102.4 ± 15.3 after blood infusion ($p = 0.07$) (Table 9).

b) Volume emptied through the pylorus (Vp)

The volume (ml/20min) emptied from the stomach was less following intragastric blood infusion being 105 ± 28.5 compared with 320.8 ± 66.2. after intragastric egg-white infusion ($p < 0.03$) (Table 9).

TABLE 8 GASTRIC SECRETORY PARAMETERS AFTER INTRAGASTRIC BLOOD AND EGG-WHITE IN 6 VOLUNTEERS

SUBJECT	ACID CONC (mmol/l)		NET H+ SEC (mmol/20min)		Hp (mmol/20min)	
NO	Egg-white	Blood	Egg-white	Blood	Egg-white	Blood
1	20.8	16.1	2.0	0.6	3.5	1.6
2	66.3	4.9	5.0	0.5	8.3	0.2
3	59.6	48.5	20.9	8.3	19.0	3.6
4	50.7	2.4	1.2	0.3	6.7	0.0
5	42.2	23.9	4.2	3.8	5.4	0.8
6	2.8	3.6	0.2	0.3	0.3	0.2
Mean	40.4	16.6	5.6	2.3	7.2	1.1
SEM	9.9	7.2	3.1	1.3	2.6	0.6
	$p < 0.05$		$p < 0.05$		$p < 0.03$	

TABLE 9 GASTRIC SECRETION AND VOLUME CHANGES AFTER INTRAGASTRIC BLOOD AND EGG-WHITE IN 6 VOLUNTEERS

SUBJECT	Vc (ml)		Vp (ml/20min)		Vs (ml/20min)	
NO	Egg-white	Blood	Egg-white	Blood	Egg-white	Blood
1	94.2	37.3	334.0	204.9	248.3	62.2
2	35.0	107.5	250.2	94.2	105.2	21.6
3	60.9	119.4	637.0	148.6	518.0	87.9
4	23.3	124.8	265.9	2.6	109.2	52.6
5	61.4	142.6	255.2	63.9	136.6	26.5
6	69.4	83.0	182.7	115.5	72.0	18.5
Mean	57.4	102.4	320.8	105.0	198.2	36.1
SEM	10.3	15.3	66.2	28.5	68.6	13.3
	$p = 0.07$		$p < 0.03$		$p < 0.03$	

Correlation between rate of emptying and rate of secretion

There was a significant positive correlation between the volume emptied through the pylorus (Vp) and net acid secretion over 20min following intragastric egg-white infusion ($r = 0.94$; $p < 0.01$) but not after blood infusion ($r = 0.21$; $p > 0.1$). There was also a significant

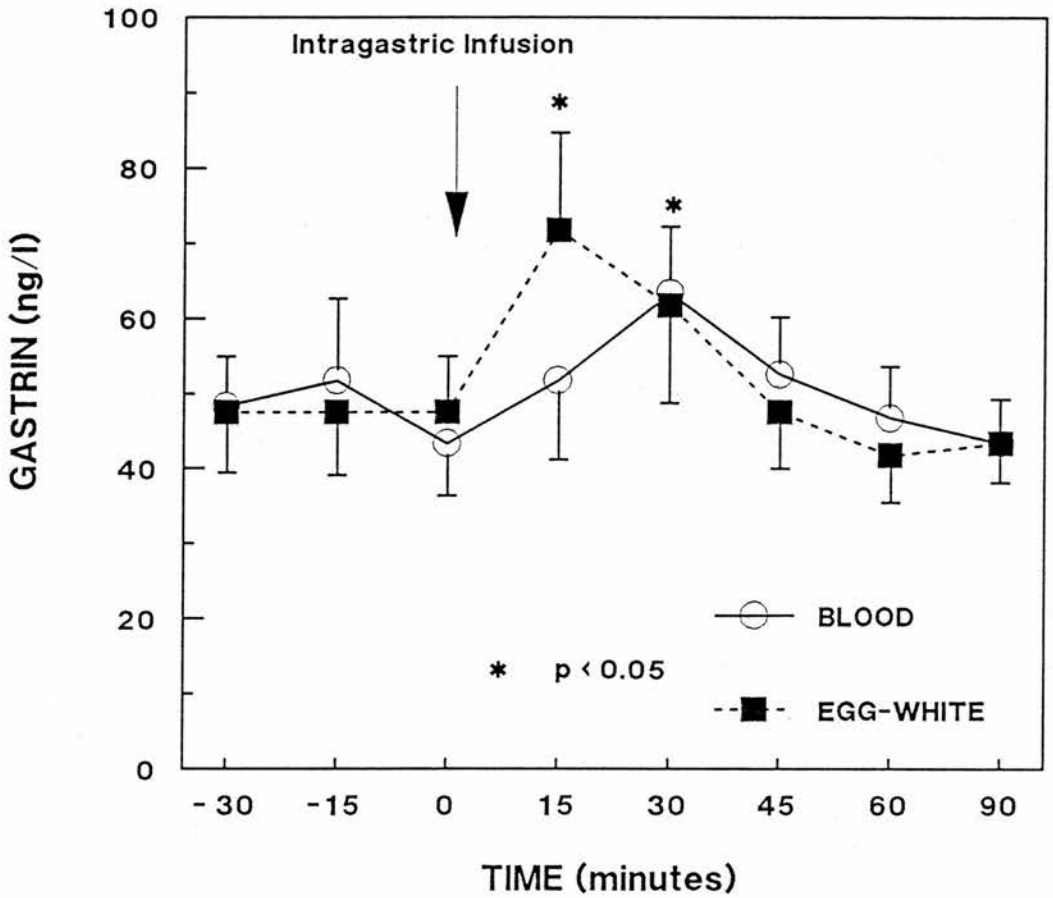


FIGURE 22

Plasma gastrin concentrations before and after intragastric infusion of blood and egg-white in 6 healthy volunteers. Results are given as Mean ± SEM.

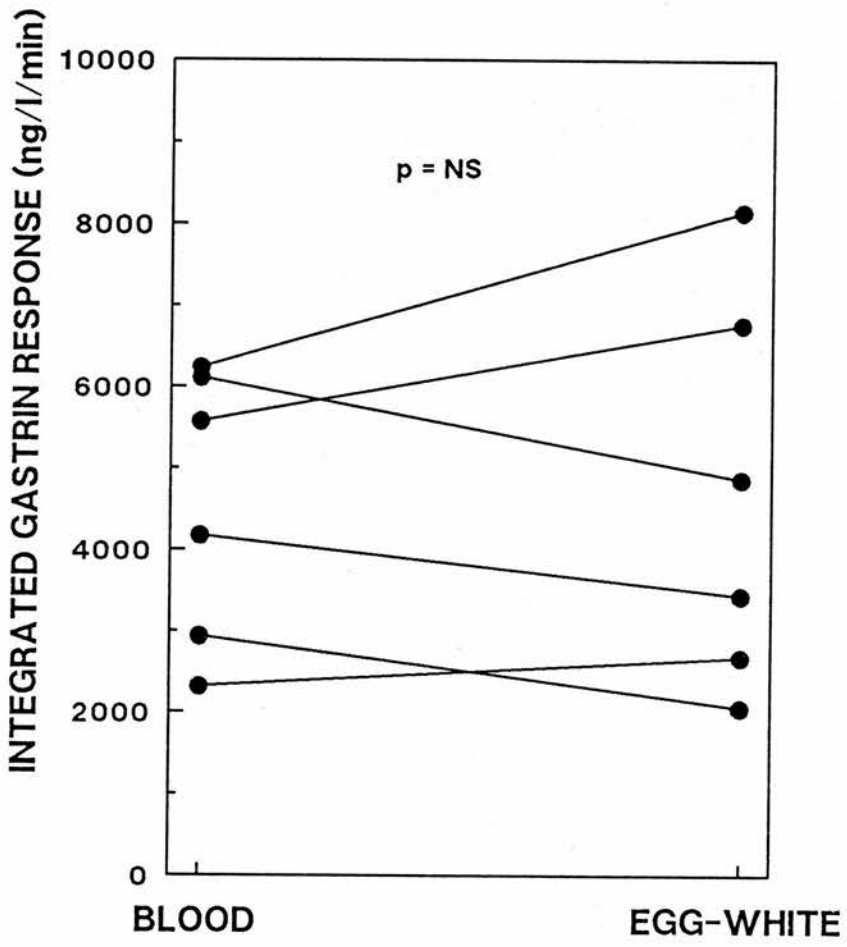


FIGURE 23

Integrated gastrin response after intragastric blood and egg-white infusion in 6 healthy volunteers.

positive correlation between the Vp and the volume secreted into the stomach over 20 minutes (Vs) after both intragastric egg-white infusion ($r = 0.99$; $p < 0.001$) and blood infusion ($r = 0.86$; $p < 0.03$).

Gastrin

Fasting serum gastrin concentrations (ng/l) were 47.8 ± 7.9 prior to intragastric blood infusion and 47.5 ± 7.8 prior to egg-white infusion ($p > 0.1$) (Fig.22). Gastrin concentrations (ng/l) increased significantly above fasting values 15 minutes after intragastric egg-white infusion at 71.7 ± 15.0 and 30 minutes after blood infusion being 63.3 ± 9.3 (Fig.22). Gastrin concentrations were significantly increased after egg-white compared with blood 15 minutes after the commencement of infusions ($p < 0.05$) (Fig.22). Integrated gastrin response (ng/l/min), however, was similar after intragastric blood infusion being 4558.4 ± 685.1 compared with 4656.2 ± 981.2 after egg-white infusion (Fig.23).

6.4 DISCUSSION

This study has demonstrated that intragastric blood infusion stimulates significantly less acid secretion and delays gastric emptying compared with an equivalent protein meal. In contrast there were no differences in the integrated serum gastrin response following either intragastric blood or egg-white infusion.

These results suggest that intragastric blood does not act as a protein meal and is not therefore a potent stimulus to acid secretion. In the context of an upper GI bleed these responses may be beneficial in promoting haemostasis.

Intragastric protein normally acts as a potent stimulus to acid secretion (BEAUMONT 1833; SAINT-HILAIRE 1960; ELWIN 1974) and serum gastrin (GROSSMAN 1967; GANGULI 1970). This stimulatory action of intragastric protein is initiated by particular amino acids and/or peptone fragments (IVY and JAVOIS 1925; ELWIN 1974) and is gastrin-mediated (WALSH et al 1971). Egg-white being essentially an albumin solution has approximately similar amino acid content to blood (ROMANOFF and ROMANOFF 1949; BRAGG and HOUGH 1961; PARKINSON 1966). It is therefore particularly surprising to demonstrate significantly less acid secretion after infusion of intragastric blood compared with egg-white. In this study intragastric blood induced a median acid secretion of 0.5mmol/20min which was 70% less than that induced by egg-white infusion (median 3.1 mmol/20min).

With intragastric egg-white infusion there was a significant positive correlation between the volume emptied into the duodenum and the rate of acid secretion. The mechanism underlying this correlation is not clear however evidence exists that intraduodenal protein may stimulate acid secretion (SIRCUS 1953; ISENBERG et al

1977) and intraduodenal acid has also been shown in duodenal ulcer subjects to stimulate acid secretion (SAUNDERS et al 1975). The absence of any correlation between the volume of intragastric blood emptied into the duodenum and acid secretion is interesting. On the basis of my previous experiments I had expected that duodenal blood would inhibit gastric acid secretion and therefore predicted a negative correlation between these parameters. In this study, however, the venous blood was heparinised and stored for a few minutes prior to intragastric infusion. It is possible therefore that the duodenal inhibitory response was mediated either through blood coagulation or some short-lived blood factor which would explain the failure to demonstrate a correlation. This may also explain the absence of any overall acid inhibition after intragastric blood. The practicalities of this study however, necessitated the use of heparinised blood.

The differences in secretion rates after intragastric egg-white and blood cannot be explained on the basis of differences in gastrin release although gastrin concentrations were significantly higher after egg-white infusion compared with blood at a single time point. This would suggest inhibitory mediation of parietal cell function either directly or indirectly by inhibition of gastrin induced acid secretion. Somatostatin is a candidate inhibitory mediator which suppresses both

gastrin-stimulated (RAPTIS et al 1975) and food-stimulated (KONTUREK et al 1976b) acid secretion possibly by a direct action on the parietal cells (BLOOM et al 1974). Other possible inhibitory mediators include the hormones of the secretin group (secretin, glucagon, GIP, VIP) which also inhibit the action of gastrin on parietal cells possibly through somatostatin release (CHIBA et al 1980; McINTOSH et al 1981; WOLFE et al 1983).

The inhibition of gastric emptying noted in this study following intragastric blood infusion compared with egg-white infusion is in agreement with the intraduodenal infusion studies. Known influences on gastric emptying of a liquid meal include the pH (SHAY and GERSHON-COHEN 1934; VAN LIERE and SLEETH 1940; HUNT and KNOX 1962), osmolality (McSWINEY and SPURRELL 1933; GERSHON-COHEN et al 1938; HUNT 1963), nutrient content (WHITE et al 1983; DOOLEY et al 1984), and volume (HUNT and McDONALD 1954) of the meal although these parameters were similar in each of the study groups. Recent evidence suggests that gastric emptying of a liquid meal may involve alteration of antro-pyloroduodenal motor activity possibly by stimulation of duodenal receptors (HOUGHTON et al 1988). Such duodenal receptors are not simply pH or osmolarity sensors but may be sensitive to other intraluminal stimuli such as glucose (MEI 1978). It is interesting to speculate that the duodenal receptors may also respond to intraluminal blood or its products to slow gastric emptying possibly mediated

by inhibitory GI hormones. In the context of upper GI bleeding reduced gastric motility is likely to be beneficial by preventing clot dislodgement, decreasing duodenal acid delivery and gastric blood flow requirements.

In conclusion, this study has demonstrated that intragastric blood infusion induces weak gastric acid secretion and inhibits gastric emptying without alteration of integrated gastrin response compared with an equivalent egg-white infusion. This suggests that contrary to expectations intragastric blood does not behave as a protein meal, an effect which may represent an additional protective mechanism in upper GI haemorrhage.

CHAPTER 7

OBSERVATIONS ON GASTRIC ACIDITY DURING UPPER GI HAEMORRHAGE

7.1 INTRODUCTION

The inhibition of gastric secretory function seen after simulated upper GI haemorrhage may represent a protective physiological response to facilitate haemostasis although confirmation that these changes occur in true upper GI haemorrhage is required. This study was designed to investigate the effect of upper gastro-intestinal haemorrhage on intragastric pH in patients with endoscopic evidence of recent or active haemorrhage.

7.2 PATIENTS AND METHODS

Patients admitted with clinical evidence of upper GI haemorrhage were routinely endoscoped within 24 hours of presentation and those with peptic ulcers which were either actively bleeding (oozing or spurting) or had stigmata of recent haemorrhage (black/red spots) were studied. Patients were classified as active haemorrhage and/or stigmata of recent haemorrhage (SRH) (Group 1). A group of six normal healthy volunteers acted as the control group (Group 2).

Following endoscopy a combined glass pH electrode (Radiometer GK 2802C) was passed perorally into the body of the stomach and its position confirmed radiologically. The pH electrode was connected to a Digitrapper MKII (Synectics Medical) solid state recorder which registers pH every 4 seconds. The electrodes were calibrated at the start of each recording period using standard buffers of

pH 1.07 (Synectics 5002) and 7.02 (Synectics 5001). Intragastric pH was monitored for 24 hours after the diagnostic endoscopy (0900-0900). In order to document intragastric blood which could increase intragastric pH by its buffering capacity an attempt was made to quantitate the intragastric blood content in those Group 1 patients actively bleeding at the time of diagnostic endoscopy. This was performed by passing a size 8 intragastric tube (Viomedex Ltd) into the body of the stomach and collecting 5ml gastric aspirates at 2 hourly intervals which were then stored for estimation of haemoglobin concentration.

All group 1 patients remained fasted and received no drug therapy during the study period. Group 2 volunteers were also studied for 24 hours but each received standard meals (700kcal each) at 12.30h and 17.30h.

Analysis

a) INTRAGASTRIC pH

The intragastric pH data were transferred from the Digitrapper MKII recorder (Synectics Medical) to an IBM compatible computer (Amstrad PC1512 HD20) and analysed using the EsopHogram and Gastrograph programs (Ver. 5.0, 1987, Gastrosoft Inc). For each group median pH profiles were created by combining individual median values at 10 minute intervals throughout the 24 hour study period using the StatpHac program (Ver. 2.07, 1987, Gastrosoft Inc).

Integrated median pH curves were then created for each study day. In addition for each individual median pH values were calculated for (a) 0900-2100 termed daytime pH, (b) 2100-0900 termed night-time pH, and (c) the entire 24 hour study period. This was facilitated by using a compatible statistical package for analysis of pH data (StatpHac, ver. 2.07, 1987, Gastrosoft Inc.). Statistical comparisons between paired data were performed for each of these study periods using the one-sided Wilcoxon Signed Rank Sum Test. Significance was taken at the 5% level ($p \leq 0.05$).

b) HAEMOGLOBIN ASSAY

This was performed with a colourimetric method using the cyanmethaemoglobin technique (Van KAMPEN and ZIJLSTRA 1961). Standardised dilutions of haemoglobin (Boehringer Corporation, London) were used to create a concentration curve. Each treated gastric sample was then analysed spectro-photometrically and its haemoglobin concentration (g/dl) estimated from the standardised curves.

Written fully informed consent was obtained in each case and all studies were approved by the local hospital Ethical Committee.

7.3 RESULTS

Six patients (5 males, 1 female, median age 56 years (range 37-68)) with peptic ulcer bleeding were studied (Group 1). The clinical and endoscopic findings in this group are shown in Table 10. Four patients from this group were actively bleeding at time of endoscopy and two had stigmata of recent haemorrhage (black/red spots).

The controls (Group 2) consisted of six healthy normal volunteers (3 males, 3 females, median age 33 years (range 26-56)).

a) Intragastric pH

The integrated pH curve for Group 1 patients revealed short periods when median pH values were significantly higher than those of the control Group 2 (Fig. 24). In Group 1 patients median daytime pH was 3.7 (range 1.2-6.8) and night-time pH 1.8 (range 1.1-7.2). The median daytime pH in Group 2 volunteers was 2.0 (1.7-3.6) and night-time pH 1.5 (1.1-2.3). Overall 24 hour median pH however was 2.8 (range 1.2-6.3) in Group 1 and 1.8 (range 1.6-2.2) in Group 2 (p = NS). In patients with duodenal ulcer the overall 24 hour median intragastric pH was 1.8 (range 1.3-2.2) and in gastric ulcers 3.5 (range 1.2-6.3).

TABLE 10 CLINICAL AND ENDOSCOPIC FEATURES OF GROUP 1 PATIENTS

PATIENT	AGE (yrs)	SEX (M/F)	NSAID's* (Y/N)	ULCER SITE (GU/DU)	ENDOSCOPIC APPEARANCE (BLEEDING/SRH)	SHOCK (Y/N)	CONTINUED BLEEDING (Y/N)	REBLEED (Y/N)	SURGERY (Y/N)
1. JG	37	M	N	DU	BLEEDING	N	N	Y	Y
2. AY	68	M	Y	GU	BLEEDING	N	N	Y	Y
3. JF	37	M	N	DU	BLEEDING	N	N	N	N
4. DD	62	M	N	GU	BLEEDING	N	N	N	N
5. ED	51	F	N	DU	SRH (black spots)	N	N	N	N
6. TC	61	M	N	GU	SRH (black spots)	N	N	N	N

*indicates non-steroidal anti-inflammatory drug intake prior to admission

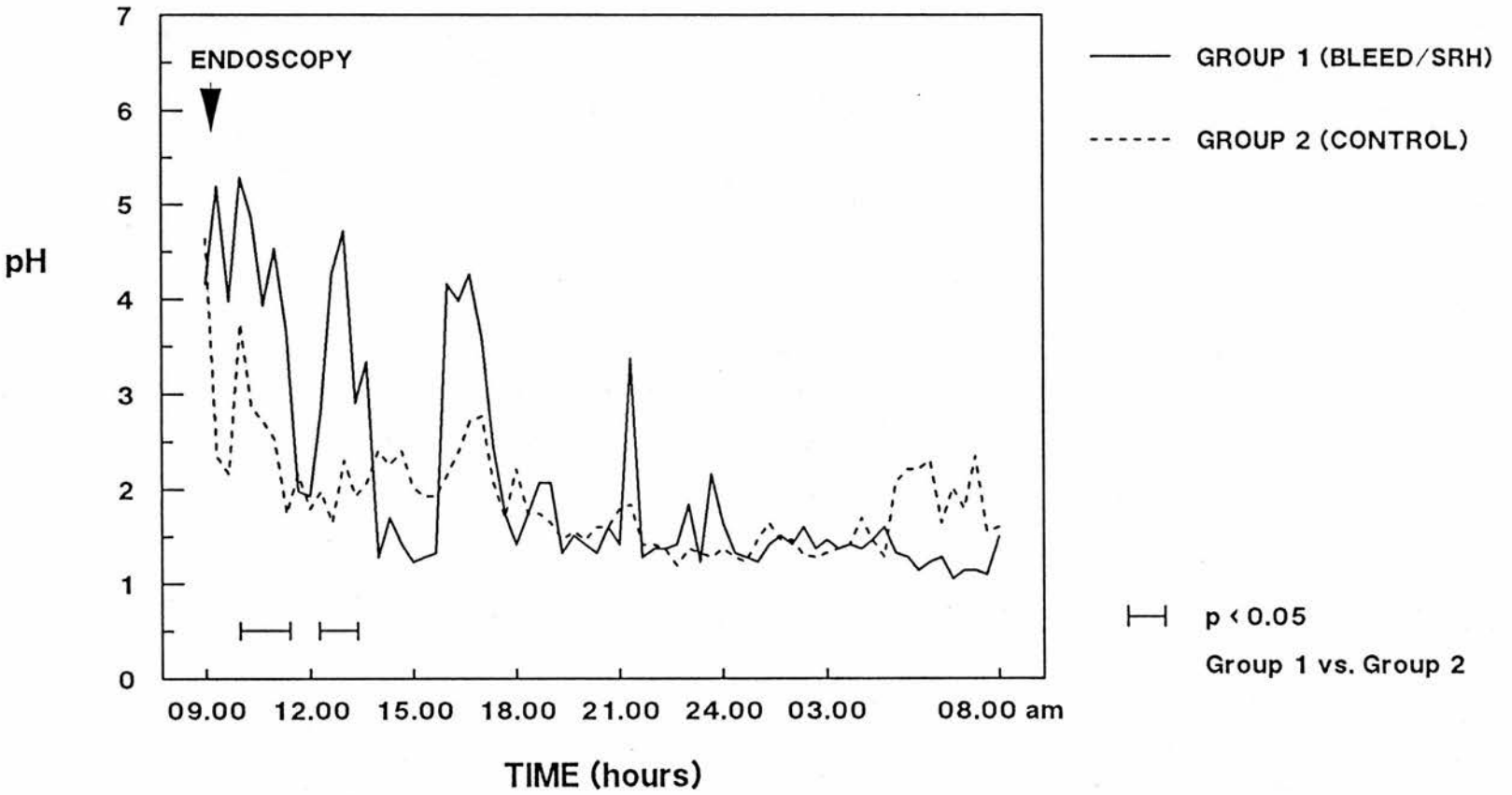


FIGURE 24 Integrated median 24 hour intragastric pH curves in 6 patients admitted with peptic ulcer haemorrhage (Group 1) and 6 healthy volunteers (Group 2).

When Group 1 patients actively bleeding at the time of endoscopy (n=4) were analysed as a separate group, the median integrated pH curve was significantly higher over longer time periods compared with the pH values for equivalent time periods in the control Group 2 (Fig.25). Each of these four Group 1 patients exhibited characteristic individual 24 hour pH curves with prolonged periods when intragastric pH rose to 7 (Figs 26 & 27). In contrast Group 1 patients with SRH only exhibited similar pH curves to Group 2 volunteers with intragastric pH remaining between 1-2 throughout the 24 hour recording period (Figs 28 & 29).

b) Haemoglobin Concentrations

None of the 4 patients with active haemorrhage at time of endoscopy had evidence of frank blood staining on gastric sampling throughout the 24 hour study period indicating the absence of continuing or recurrent haemorrhage during this period. In addition, haemoglobin concentrations also remained low throughout the study period (Table 11) at levels which from my previous in-vitro work (Chapter 5) could not have altered intragastric pH by buffering alone.

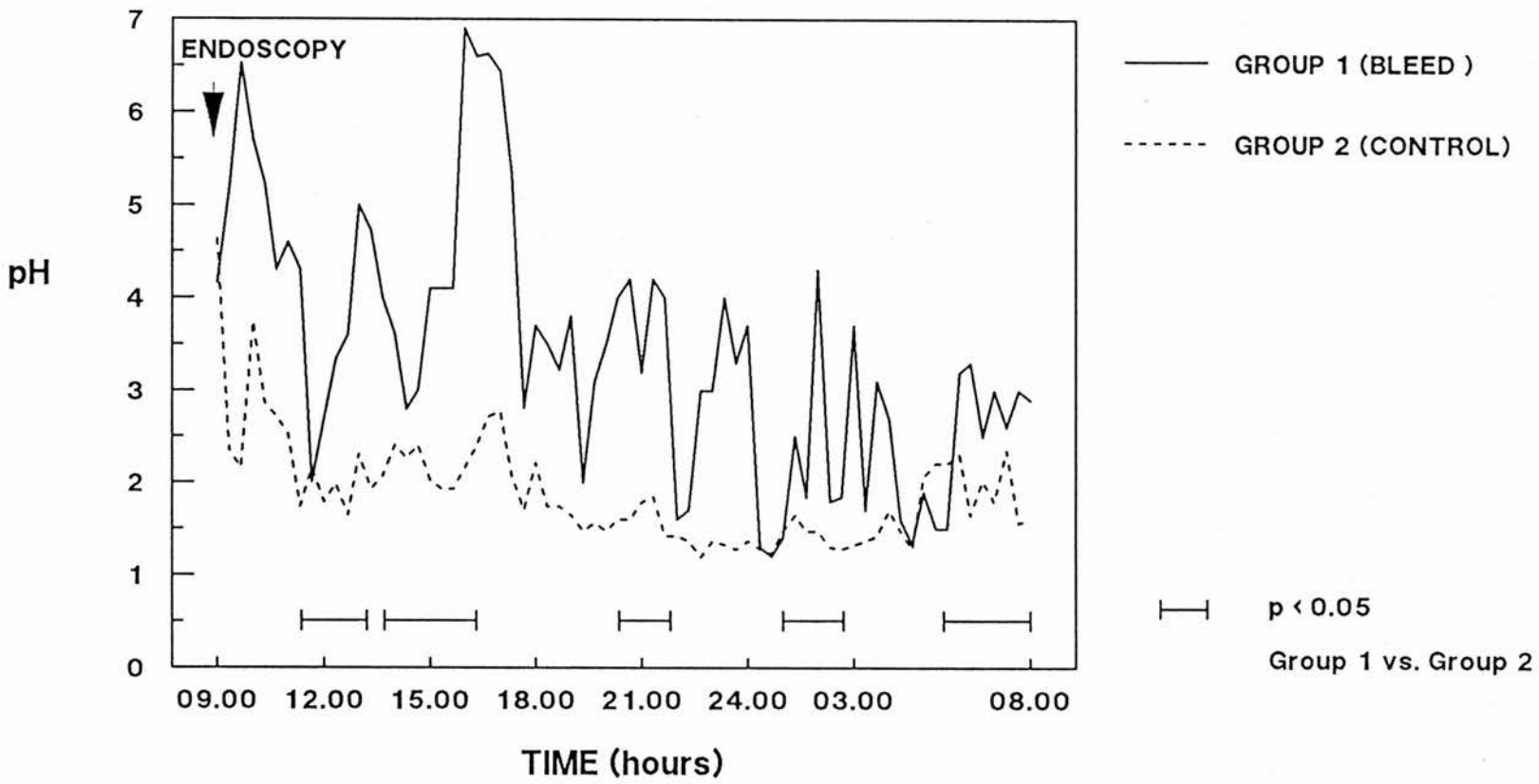


FIGURE 25 Integrated median 24 hour intragastric pH curves in 4 Group 1 patients with active peptic ulcer haemorrhage and 6 healthy volunteers (Group 2).

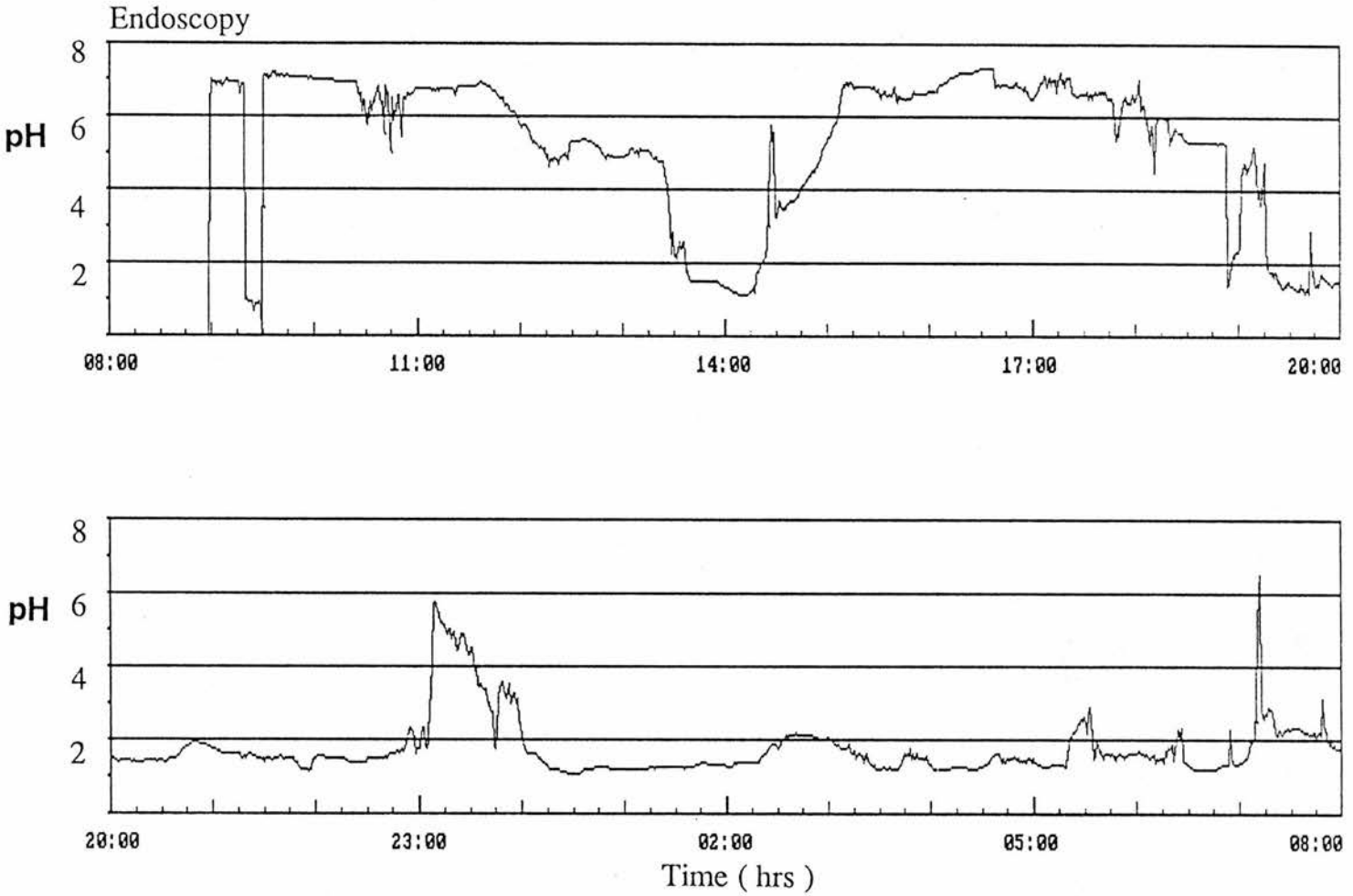


FIGURE 26 24 hour intragastric pH recording in a 37 year old male patient actively bleeding at time of endoscopy from a duodenal ulcer, demonstrating prolonged periods of high intragastric pH.

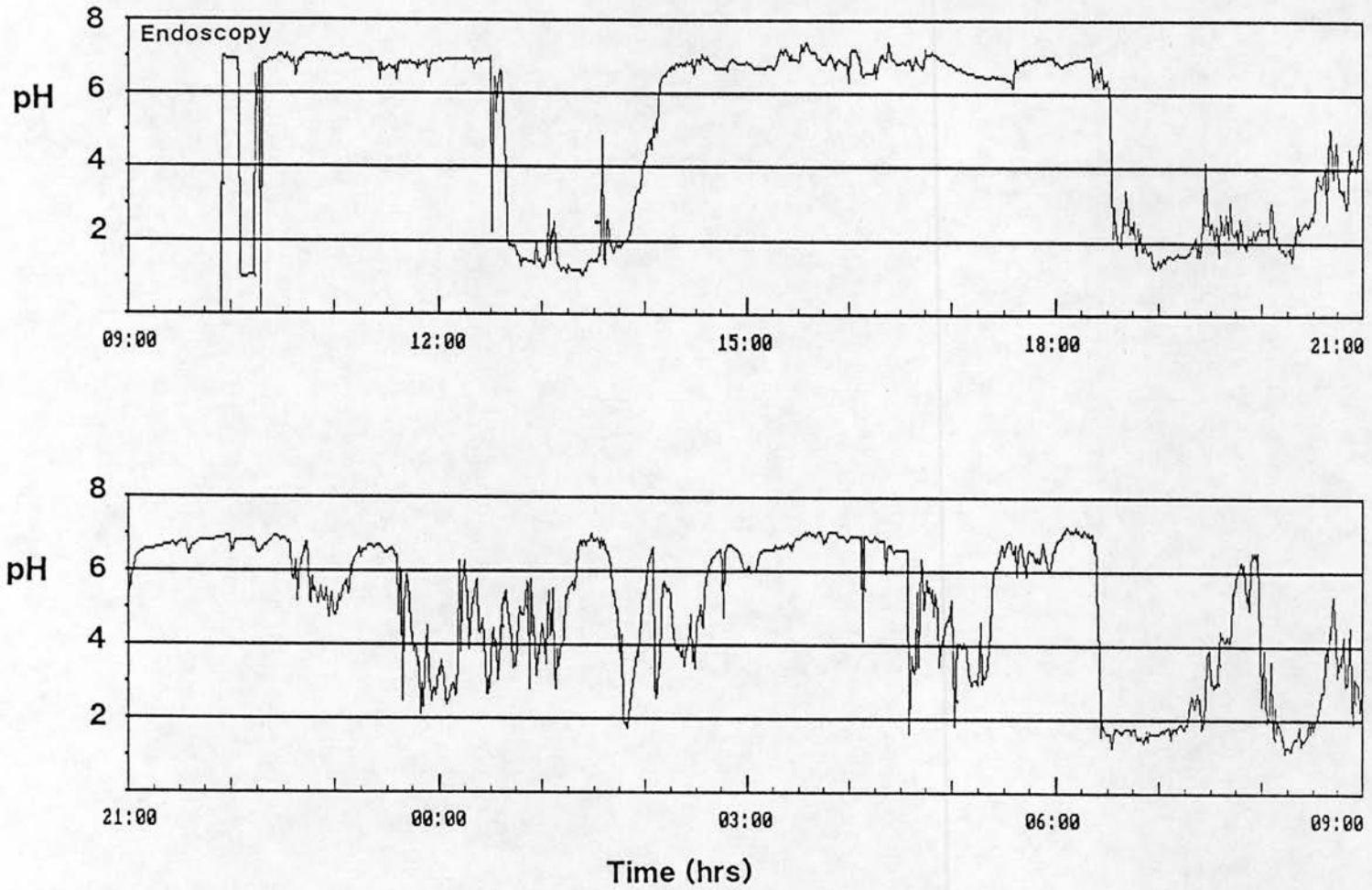


FIGURE 27 24 hour intragastric pH recording in a 62 year old male patient actively bleeding at time of endoscopy from a gastric ulcer, demonstrating prolonged periods of high intragastric pH.

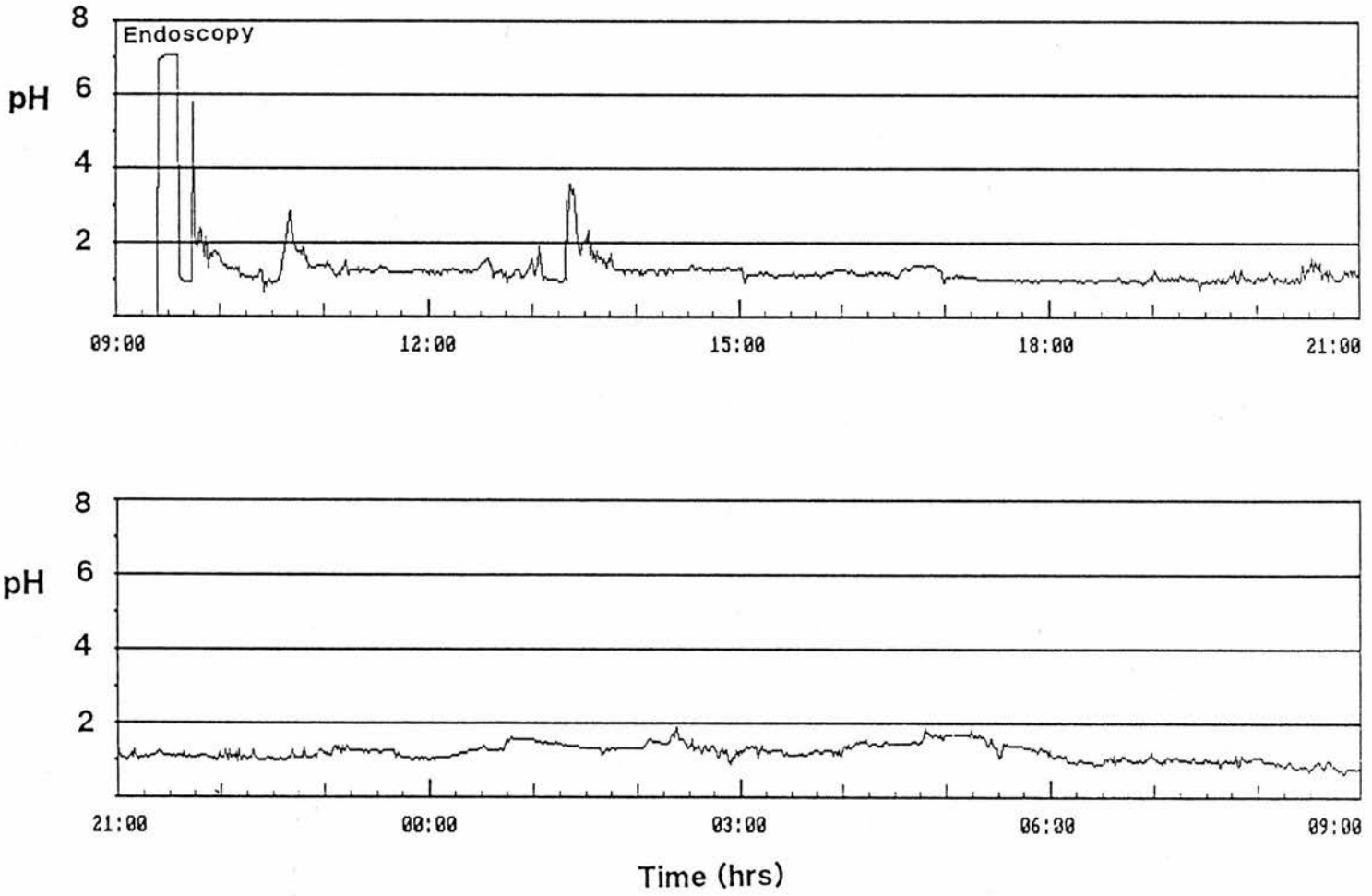


FIGURE 28 24 hour intragastric pH recording in a 61 year old male gastric ulcer patient with only minor stigmata of recent haemorrhage at endoscopy, demonstrating normal pH range.

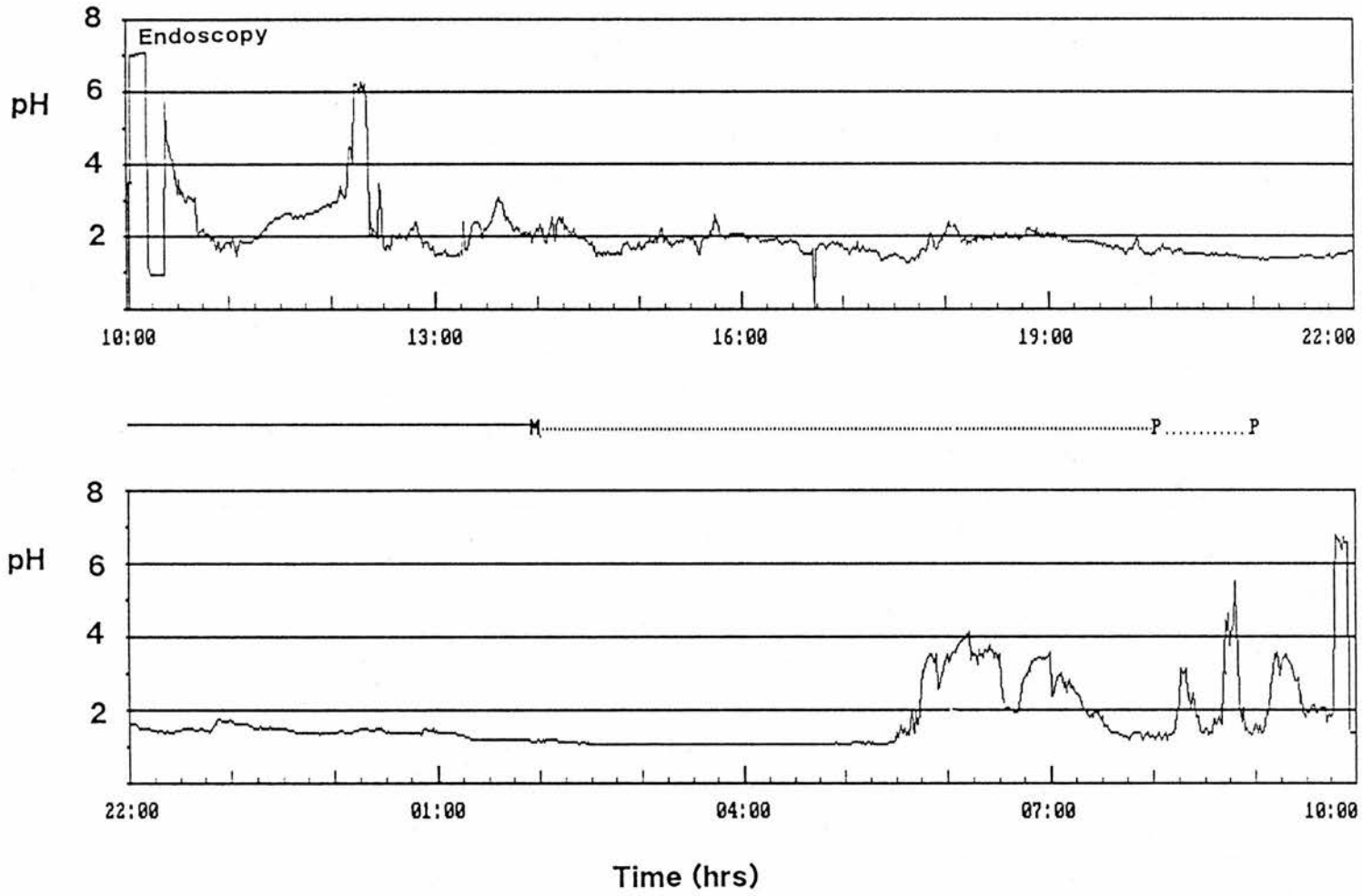


FIGURE 29 24 hour intragastric pH recording in a healthy 35 year old volunteer demonstrating normal pH range.

TABLE 11 INTRAGASTRIC HAEMOGLOBIN CONCENTRATIONS (g/dl) IN GROUP 1 PATIENTS ACTIVELY BLEEDING AT TIME OF ENDOSCOPY

	TIME (hours)									
PAT	1400	1600	1800	2000	2200	2400	0200	0400	0600	0900
1	0.88	0.42	0.05	0.06	0.33	0.01	0.54	0.33	0.20	0.07
2	0.08	0.06	0.00	0.02	0.02	0.04	0.02	0.11	0.01	0.03
3	0.15	0.05	0.87	0.07	0.00	0.01	0.02	0.04	0.02	0.00
4	0.12	0.20	0.60	0.10	0.15	0.30	0.30	0.20	0.20	0.10
Mean	0.31	0.18	0.38	0.06	0.12	0.09	0.22	0.17	0.11	0.05
SEM	0.19	0.09	0.21	0.02	0.08	0.07	0.12	0.06	0.05	0.02

c) Correlation of Intragastric pH with Hydrogen Ion Concentration of aspirated Gastric Juice in 2 Patients Actively Bleeding from Peptic Ulcers

In order to further eliminate intragastric blood clot or duodenogastric reflux as a cause of the high intragastric pH in patients actively bleeding, 5ml aliquots of gastric juice were collected in 2 Group 1 patients (1 and 2) at 2 hourly intervals throughout the 24 hour study period for estimation of hydrogen

ion activity. Titratable acidity was calculated by autotitration (Radiometer ETS 822) to pH 7 using 0.1 N sodium hydroxide.

In both patients intragastric contents remained anacid for 8 hours (Table 12). In patient 1 intragastric acidity increased after 10 hours to 55.6 mmol/l and remained at high basal acid concentrations until 6.00am the next day. These concentrations corresponded well with his intragastric pH recordings (Fig.26). Patient 2 remained effectively achlorhydric for the entire 24 hour recording period (Table 12) again corresponding well with the intragastric pH recordings (Fig.27).

TABLE 12 TITRATABLE ACIDITY (mmol/l) OF ASPIRATED GASTRIC JUICE IN 2 PATIENTS WITH ACTIVELY BLEEDING PEPTIC ULCERS

	TIME (hours)										
PAT	10am	12	2	4	6	8	10	12	2	4	6am
1.JG	0	0	0	0	2.4	55.6	77.9	81.9	55.0	33.9	41.3
2.AY	0	0	0	0	0	3.6	0	2.2	0	0	0

7.4 DISCUSSION

This study has demonstrated that in patients actively bleeding from peptic ulcers there were prolonged periods during the following 24 hours where intragastric pH was elevated compared to a healthy control group. Moreover although these patients were actively bleeding at the time of endoscopy subsequent regular gastric aspirates indicated a low concentration of intragastric blood suggesting the bleeding had stopped and minimising the possibility of any simple buffering effect. In the absence of active bleeding however, intragastric pH remained similar to that of healthy volunteers.

The demonstration of raised intragastric pH often to neutrality (pH 7) during active peptic ulcer bleeding suggests a marked inhibition of gastric acid secretion. This finding is in agreement with the original demonstration of acid inhibition following simulated intraduodenal haemorrhage and with Chandler & Watkinson's observations in clinical upper GI bleeding (CHANDLER and WATKINSON 1959). The very low levels of intragastric haemoglobin concentrations throughout the 24 hour recording period adds further supporting evidence to acid inhibition rather than a blood buffering effect being the cause of the observed increase in intragastric pH. In addition, the demonstration of long periods of achlorhydria by gastric aspiration makes duodenogastric reflux less likely as a cause for the periods of high

intragastric pH, although confirmation of this by estimation of sodium concentration requires further study. The absence of hypovolaemic shock in the study group also excludes the possibility that these changes in intragastric pH were due to shock induced inhibition of gastric function (STANNARD et al 1988).

These studies also add further evidence to the estimated duration of this acid inhibitory effect after upper GI bleeding. In one patient actively bleeding at the start of pH recording the intragastric pH was noted to return to normal values after approximately 12 hours (Fig.26) while in others it remained elevated up to 24 hours later (Fig.27). This suggests the effect lasts for up to 12 hours and may persist for at least 24 hours which is in broad agreement with my experimental studies in Chapter 3. It may be relevant however that the early return of normal intragastric pH in patient 1 was followed by a significant rebleed 60 hours later requiring surgical intervention. It is interesting to speculate that this early return of normal intragastric pH may have represented the loss of the protective acid inhibitory response and predisposed to rebleeding.

Although the control group used in this study was not fasted, food has only a short-lived effect on gastric pH by way of its buffering capacity (McLAUGHLAN et al 1988). It was felt therefore that the groups were broadly comparable. In addition, the intragastric pH ranges in

the volunteer group used in this study were similar to those demonstrated in duodenal ulcer subjects (BENDTSEN et al 1987; FULLARTON et al 1988).

A previous study monitored the effects of intravenous cimetidine and ranitidine on 24 hour intragastric pH in patients with peptic ulceration admitted with upper GI bleeding (REYNOLDS et al 1987). In those duodenal ulcer patients randomised to receive placebo median intragastric pH was 1.8 (range 1.0-4.9). This study, however, assessed only patients with SRH and the authors do not comment on whether any patients were actively bleeding at the time of endoscopy. Although only one patient in this study required surgery for rebleeding it was of interest to note that his 24 hour median pH was 1.8 despite ranitidine therapy. This also suggests that an early return of normal acidity or a failure of H2 receptor antagonist therapy to maintain a high intragastric pH may represent an adverse prognostic sign in peptic ulcer haemorrhage.

In conclusion intragastric pH is elevated in patients during active peptic ulcer bleeding, an event which occurs without high concentrations of intragastric blood. This further suggests that gastric secretory function is inhibited in the early phase of peptic ulcer haemorrhage which may represent an early protective mechanism to facilitate haemostasis and clot stabilisation.

CHAPTER 8

THE EFFECT OF UPPER GI HAEMORRHAGE ON GI HORMONES

8.1 INTRODUCTION

My earlier experimental studies have suggested that the acid and pepsin inhibition and decreased gastric emptying seen following simulated upper GI haemorrhage may have been mediated by gastric inhibitory peptide (GIP), a candidate enterogastrone. This study was therefore designed to examine the effects of true upper GI haemorrhage on GI hormones to determine whether similar changes occur.

8.2 PATIENTS AND METHODS

Eight patients, 6 males, 2 females - median age 74 years (range 69-76), presenting to the Western Infirmary Haematemesis Management Team with upper GI haemorrhage, (documented haematemesis and/or melaena) were studied. All patients were fasted for at least 6 hours before study and all underwent upper GI endoscopy within 24 hours of presentation to accurately identify the source of haemorrhage. Potentially eligible patients for this study had an identifiable lesion in the upper GI tract with either active haemorrhage or stigmata of recent haemorrhage at endoscopy. When a patient was deemed eligible for study entry 10ml of venous blood was removed (time 0) from a forearm vein and added to heparinised tubes. Each sample was then immediately centrifuged, the plasma removed and stored at -20 degrees Centigrade for later GI hormone assay. Repeat venous blood samples were

taken at 4 hourly intervals during the day and at 6 hourly intervals during the night until time 24 hours. All patients remained fasted throughout this 24 hour period. Patients were managed by members of the HMT and 6 received H2 receptor antagonist therapy (IV Ranitidine 50mg 6 hourly) during the study period. Rebleeding and requirement for surgery were decided independently by a member of the HMT who was not involved in the GI hormone study. The clinical and endoscopic features of the study group are shown in Table 13.

TABLE 13 CLINICAL AND ENDOSCOPIC FEATURES OF STUDY GROUP

PAT	AGE (Years)	SEX (M/F)	BLEEDING SOURCE	NSAID* (Y/N)	SHOCK (Y/N)	REBLEED (Y/N)	SURG (Y/N)
AH	69	M	DU	Y	N	N	N
WC	76	M	Oesoph.Varices	Y	N	N	N
JA	75	M	Oes. ulcer	N	N	N	N
SM	73	F	Gastric Eros.	Y	N	N	N
AR	76	M	DU	N	Y	N	N
AF	76	F	Gastric Eros.	Y	N	Y(3/7)	N
RC	73	M	Varices	N	N	Y(3/7)	N
JO	73	M	Oes. ulcer	N	N	N	N

* Non steroidal anti-inflammatory drug intake prior to admission

Hormone Assay

The following GI hormones with known effects on gastric secretion and/or motility were studied - GIP, gastrin, VIP and neurotensin. Each sample was analysed by individual radio-immunoassay (Appendix) by Professor K. Buchanan's laboratory, Department of Medicine, Queens University, Belfast.

Analysis

Individual hormone values for each time period studied after admission were plotted and compared with the laboratory's upper limit of normal for fasting patients (based on mean + 2SD for normal healthy fasting volunteers). For each patient the median 24 hour GI hormone concentration was also calculated and termed 24 hour hormone concentration.

8.3 RESULTS

Each patient had a median number of 4 (range 3-5) samples taken over the first 24 hours of admission with upper GI bleeding.

1) GIP

GIP concentrations were consistently elevated above the normal range over the 24 hour study period in all but two samples (Fig.30). The median 24 hour GIP concentration (ng/l) for the 8 patients ranged from 105-260 (median 140) compared with the normal range of 0-100ng/l.

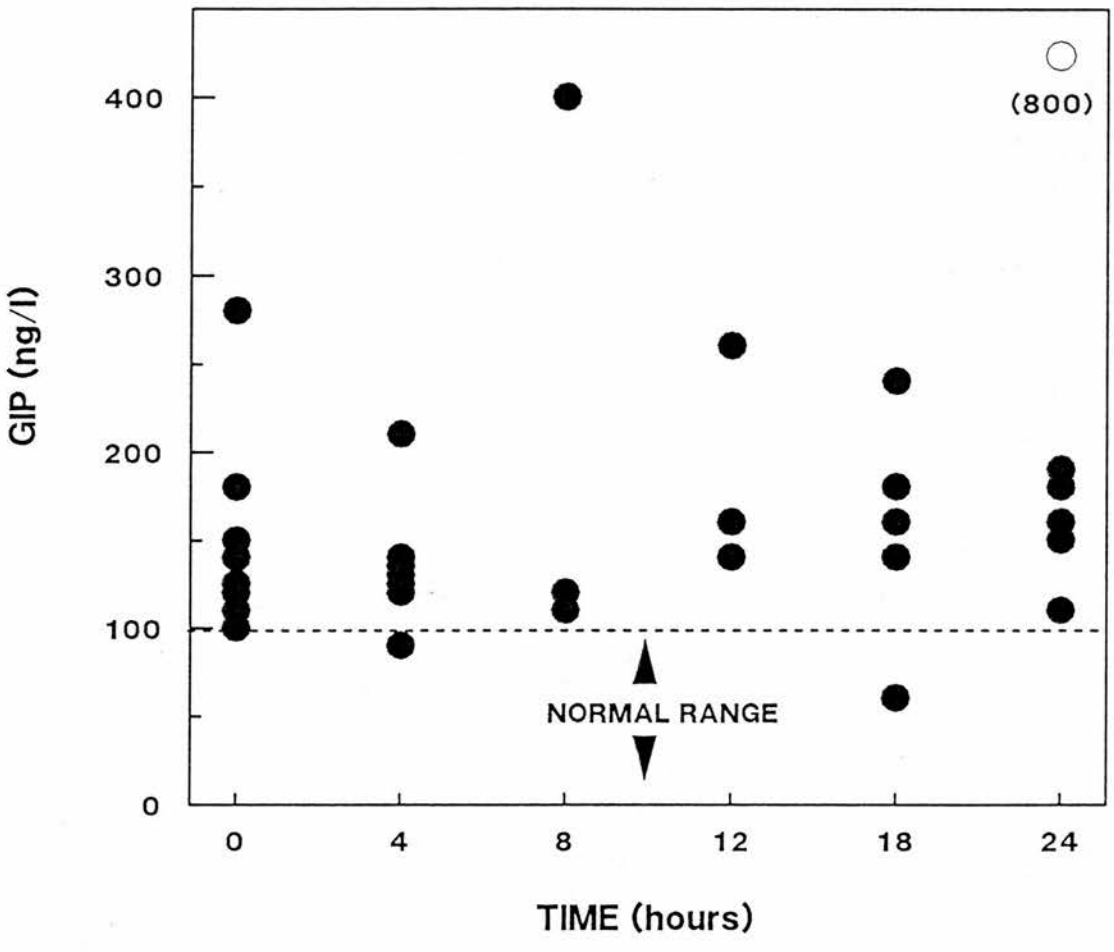


FIGURE 30

Plasma GIP concentrations during the 24 hours following endoscopy in 8 patients admitted with acute upper GI haemorrhage. Dotted line represents laboratory's upper limit of normal.

2) Gastrin

All fasting gastrin concentrations were within the normal range over the 24 hour study period (Fig.31). The median 24 hour gastrin concentration (ng/l) for the 8 patients ranged from 10-43 (median 33) compared with the normal range of 0-100ng/l.

3) Neurotensin

Neurotensin concentrations were consistently within the normal range over the 24 hour study period (Fig.32). The median 24 hour neurotensin concentration (ng/l) for the 8 patients ranged from 10-15 (median 12) compared with the normal range of 0-20ng/l.

4) VIP

All VIP concentrations were within the normal range over the 24 hour study period (Fig.33). The median 24 hour VIP concentration (ng/l) for the 8 patients ranged from 10-55 (median 29) compared with the normal range of 0-100ng/l.

8.4 DISCUSSION

This study has shown that fasting GIP concentrations are elevated in patients admitted with acute upper gastrointestinal haemorrhage. This adds further evidence to the earlier experimental finding of elevated GIP

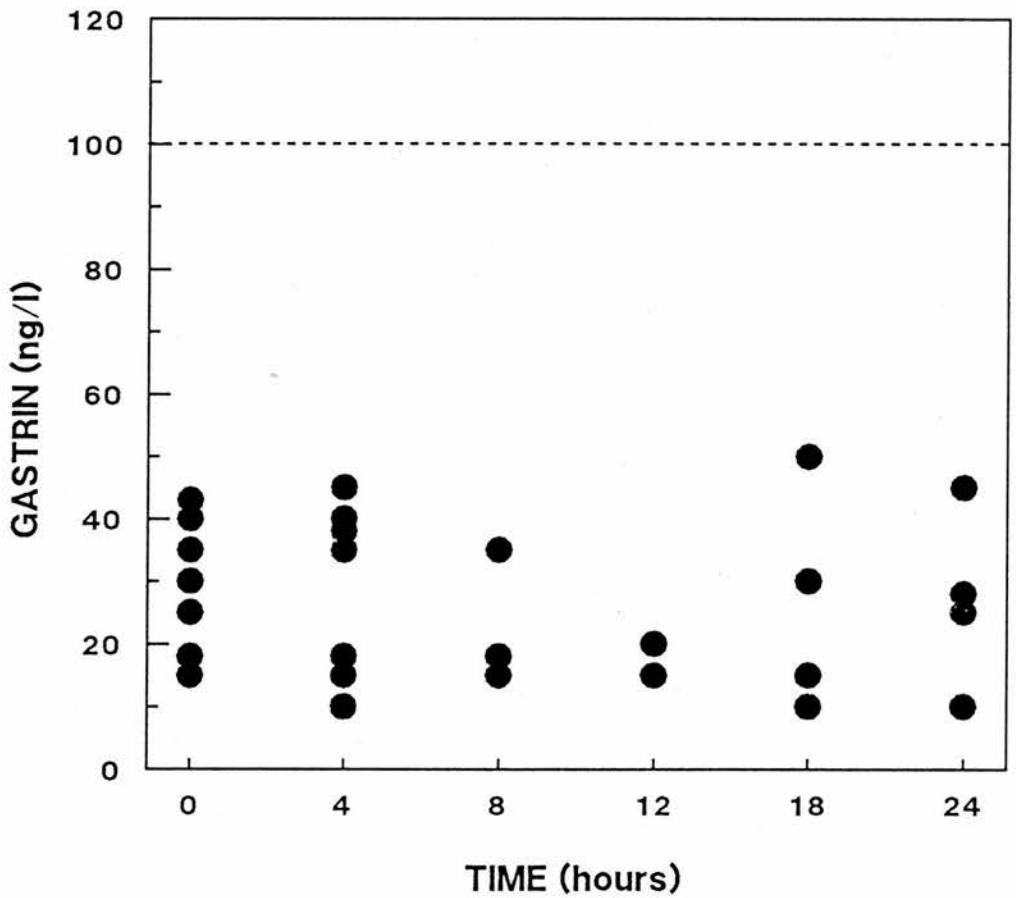


FIGURE 31

Plasma gastrin concentrations during the 24 hours following endoscopy in 8 patients admitted with acute upper GI haemorrhage. Dotted line represents laboratory's upper limit of normal.

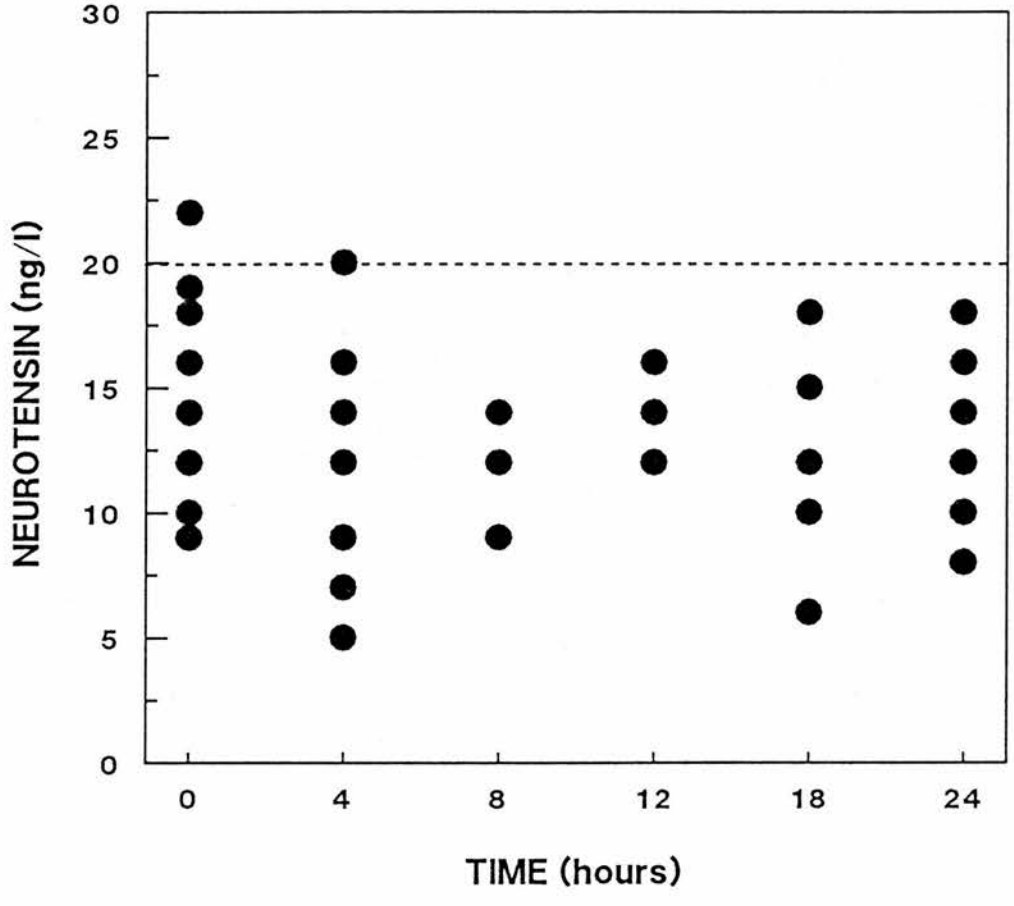


FIGURE 32

Plasma neurotensin concentrations during the 24 hours following endoscopy in 8 patients admitted with acute upper GI haemorrhage. Dotted line represents laboratory's upper limit of normal.

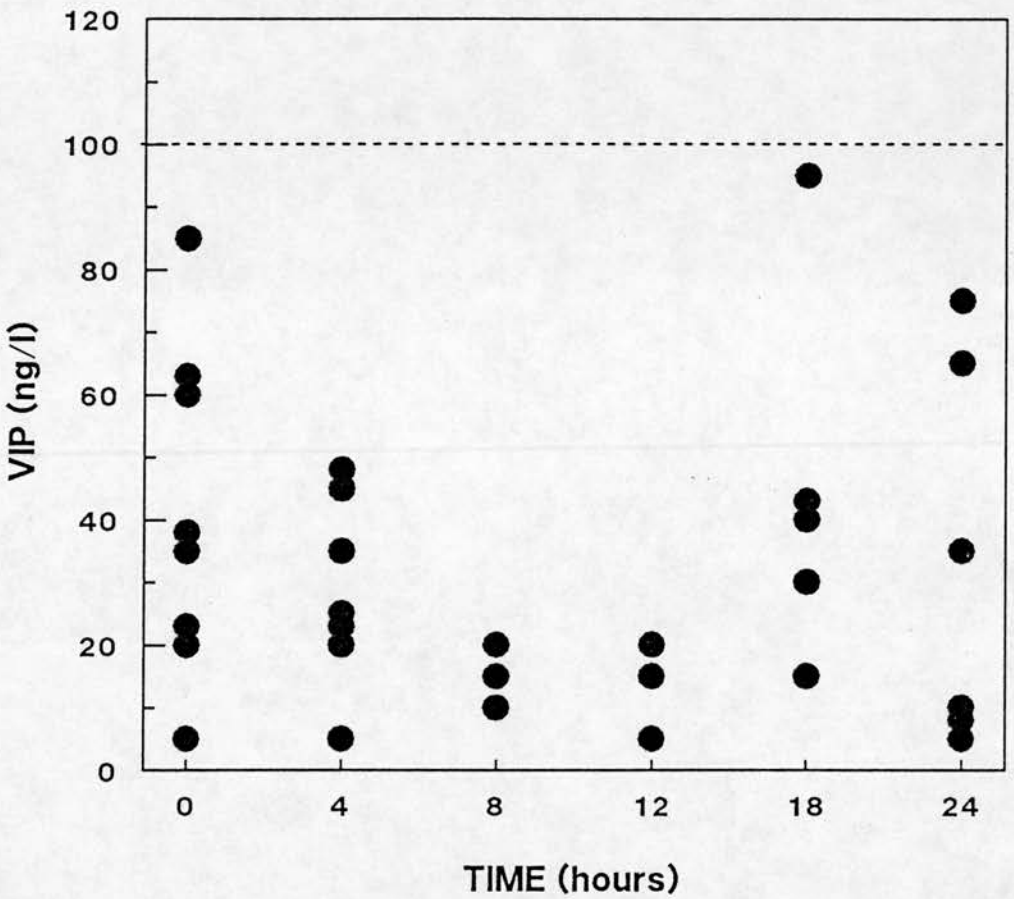


FIGURE 33

Plasma VIP concentrations during the 24 hours following endoscopy in 8 patients admitted with acute upper GI haemorrhage. Dotted line represents laboratory's upper limit of normal.

concentrations after simulated intraduodenal haemorrhage suggesting intraluminal blood may act as a stimulus to GIP secretion.

GIP was originally isolated from an impure preparation of cholecystokinin which had been shown to produce less stimulation of acid secretion than a purer preparation (BROWN and PEDERSON 1970). It was later purified (BROWN et al 1970) and localised to the duodenum and jejunum (POLAK et al 1973; BUFFA et al 1975) in specific endocrine cells classified as K-cells (BUCHAN et al 1978). Although the known intraduodenal stimuli to GIP release include glucose (THOMAS et al 1977) fat (LUCEY et al 1984), amino acids (THOMAS et al 1978) and acid (LE ROITH et al 1980), the only known physiological effect of GIP relates to its insulinotropic action (PEDERSON et al 1975; ANDERSEN et al 1978). The enterogastrone effect, however, remains controversial and incompletely understood in man (FLATEN 1983) although this effect may be mediated by gastric somatostatin release (McINTOSH et al 1981).

The specific increase in GIP concentrations seen in this study after GI bleeding is interesting and may be relevant to the observed alterations in gastric acid secretion seen after simulated upper GI haemorrhage and the increases in gastric pH seen in clinical upper GI haemorrhage. A non-specific effect of intraluminal blood is unlikely as the GIP increase was unique and other candidate hormones released by the duodenum and jejunum

remained unaltered. In this study GIP concentrations remained elevated above normal fasting values for the entire 24 hour study period suggesting continued release despite the relatively long plasma half-life of 20 minutes (SARSON et al 1982). If intraluminal blood, however, acts as a stimulus to GIP secretion, then continued prolonged secretion may be expected as all the study patients had evidence of fresh blood in the upper GI tract at endoscopy which would persist in the small bowel for at least several hours. In addition, my previous studies have suggested that GI motility may be inhibited by intraluminal blood which may further prolong a luminally mediated response. The present study, however, was uncontrolled and confirmation that these increases are truly specific to upper GI bleeding await further controlled studies.

In conclusion I have observed specific increases in GIP concentrations in patients admitted with upper GI bleeding adding further evidence to suggest intraluminal blood may be a stimulus to its release.

CHAPTER 9

PREDICTION OF REBLEEDING IN PEPTIC ULCERS - BY VISUAL STIGMATA AND ENDOSCOPIC DOPPLER ULTRASOUND CRITERIA

9.1 INTRODUCTION

The mortality rate of acute upper gastrointestinal haemorrhage remains at 10% due mainly to rebleeding in an increasingly elderly population (ALLAN & DYKES 1976; MORGAN et al 1977; HUNT et al 1979). Early identification of patients at high risk of rebleeding with subsequent prompt therapy (endoscopic or surgical) may lead to an improvement in the rebleeding and mortality rates for peptic ulcer.

At present the prediction of recurrent haemorrhage relies on clinical and endoscopic criteria. Clinical factors based on age or the severity of the presenting bleed have been used to predict rebleeding and at best may be correct in 70% of patients (MORGAN et al 1977; MacLEOD et al 1982; BORNMAN et al 1985). Endoscopic prediction relies on the diagnosis of visible stigmata of recent haemorrhage (SRH) (FOSTER et al 1978) and in particular on the presence of a visible vessel in the ulcer base (GRIFFITHS et al 1979). There is, however, controversy over the endoscopic appearances of a visible vessel and its significance with published rebleeding rates in the visible vessel group of 32-100% (GRIFFITHS et al 1979; STOREY et al 1981; MacLEOD and MILLS 1982; WARA 1985). In addition, rebleeding as a result of a visible vessel, accounts for a variable proportion (28-95%) of all rebleeds in published series (GRIFFITHS et al 1979; STOREY et al 1981). Consideration of both clinical and

endoscopic features however, may allow better determination of outcome than either factor alone (BREARLEY et al 1987a).

There is clearly therefore a need for further definitive criteria allowing early prediction of rebleeding and early therapeutic intervention. The aim of this study was to establish the significance of a patent arterial vessel in a peptic ulcer base as detected by transendoscopic Doppler Ultrasound in an attempt to improve prediction of rebleeding.

9.2 PATIENTS AND METHODS

All patients admitted to the Western Infirmary, Glasgow with acute upper GI haemorrhage over the 18 month period of the trial (August 1986-January 1988) were considered for inclusion. Patients presenting with haematemesis and/or melaena were routinely endoscoped within 24 hours of admission by an experienced member of the Haematemesis Management Team (HMT). Potentially eligible patients were diagnosed endoscopically to have a single peptic ulcer in the stomach, pyloric canal or duodenal cap.

When a patient was recognised to be potentially eligible for study entry the ulcer was assessed by the TVD endoscopist (myself). The patient was only deemed eligible for entry into the study if the following criteria were also met:

a) actively bleeding sites on the ulcer before or after washing and/or

b) a visible vessel in the ulcer base before or after washing and

c) confirmed accessibility of the TVD probe to the ulcer site.

Active bleeding was defined as a continuous flow of blood from the ulcer base continuing for the duration of the endoscopy. A visible vessel was defined as an elevated red or blue spot, a pulsatile pseudoaneurysm or active arterial spurting.

Patients who fulfilled these criteria were then entered into the study and each ulcer base screened with the transendoscopic vascular detector probe (TVD-1, outer diameter 2.5mm, KeyMed Ltd., Southend-On-Sea), using an Olympus IT10 gastroscope (Olympus Corp, Japan). Five separate recordings were taken from each ulcer base i.e. 4 at 90 degree intervals around the ulcer periphery and one in the centre. The output was transmitted through headphones and a positive signal recorded if an unequivocal pulsatile sound was heard at a localised area of the ulcer base, which disappeared on minor movement of the transducer. Larger deeper vessels such as the aorta or left gastric artery could also be detected using the TVD probe although such signals persisted despite minor probe movement unlike more superficially placed vessels

(BECKLY and CASEBOW 1986). Each patient's Doppler information was only available to the TVD endoscopist (myself) and he took no further part in their management.

Following endoscopy patients were managed by members of the HMT unaware of the Doppler findings and their progress documented until discharge or death. Rebleeding was diagnosed by HMT members if one of the following features was present.

a) fresh blood in the upper gastrointestinal tract (UGIT) at re-endoscopy or surgery.

b) vomiting fresh blood at any time other than immediately after endoscopy where fresh blood had been noted in the UGIT.

c) fresh melaena plus <u>one</u> of the following:

   1. haemodynamic and clinical evidence of hypovolaemic shock (systolic BP < 100, pulse rate > 100).

   2. a falling Hb despite blood transfusion. (Failure to raise Hb by more than 0.5g/dl per unit of blood transfused).

Surgical intervention for haemostasis was undertaken when deemed appropriate by the attending HMT surgeon.

9.3 RESULTS

During the 18 month trial period (August 1986-January 1988) 711 patients presenting with suspected acute upper gastrointestinal haemorrhage were endoscoped within 24 hours of presentation to the Western Infirmary, Glasgow. 180 (25%) were found to have a peptic ulcer. 124 (69%) had either no stigmata of recent haemorrhage (SRH) or minor SRH (flat black/red spots) at the time of endoscopy. This group was deemed a low risk group in terms of rebleeding but their progress was also documented until discharge. In the initial stages of this study ten patients from this group also underwent TVD assessment. None of these 124 patients rebled and none of the 10 patients assessed had positive Doppler signals from their ulcer bases. 56 patients had a single peptic ulcer with either active haemorrhage or a visible vessel and 22 were entered into the trial. There were 34 exclusions due mainly to patient recruitment to a concomitant heater probe study (Table 14). The clinical and endoscopic features of the twenty two patients entered into the study are shown in Tables 15 and 16. Ten had active oozing from the ulcer base, 9 had visible vessels in the ulcer base and three had clot resistant to washing. Eight of the 9 visible vessels were not bleeding at the time of endoscopy, 1 showed non-pulsatile active bleeding. Overall nine patients (41%) rebled, seven (32%) required surgery and one died (5%). Of the 9 patients who rebled,

8 had a visible vessel in the ulcer base giving a sensitivity for this endoscopic feature of 89%. Only one patient without a visible vessel (ulcer base oozing) rebled, giving a specificity for visible vessel rebleeding of 92%.There were 6 rebleeds from duodenal ulcers (all postero-inferior in position) and 3 rebleeds from gastric ulcers (2/3 high lesser curve in position).

Eight of the twenty two patients assessed were Doppler positive (36%) and of these 7 rebled giving a sensitivity of 87% (Table 17). Two patients who were Doppler negative rebled giving a specificity for this investigation of 12/14 (86%).

When the presence of a visible vessel and a Doppler positive signal were assessed together to predict rebleeding the sensitivity was increased to 100% (Table 17). All patients therefore, with an endoscopic visible vessel and a Doppler positive signal rebled.

TABLE 14 **EXCLUSIONS (n = 34)**

Entered into heater probe study	20
Inaccessibility	5
TVD endoscopist absent	4
Equipment failure	4
Torrential haemorrhage	1
TOTAL	34

TABLE 15 **STUDY ENTRY CLINICAL CHARACTERISTICS (n=22)**

Age	56.9 ± 4.8 *
Admission Hb(gdl -1)	10.6 ± 0.6 *
Shocked on admission (systolic BP ≤ 100, pulse > 100)	6
Pre-endoscopy blood transfusion (units packed cells)	1.6 ± 0.4 *

* Mean ± SEM

TABLE 16 **ULCER CHARACTERISTICS (n = 22)**

Ulcer Site	
GU	6
DU	16
Endoscopic Features	
Clots	3
Active Oozing	10
Visible Vessel	9

TABLE 17 **PATIENTS REBLEEDING**

SRH	DOPPLER +ve	DOPPLER -ve	TOTAL REBLEEDS
CLOT	0/1 (0%)	0/2 (0%)	0/3 (0%)
VISIBLE VESSEL	7/7 (100%)	1/2 (50%)	8/9 (89%)
ACTIVE OOZING	0/0 (0%)	1/10(10%)	1/10(10%)
TOTAL	7/8 (87%)*	2/14(14%)	9/22(41%)

*$p < 0.05$

9.4 DISCUSSION

This study has demonstrated that the Doppler ultrasound can predict rebleeding in peptic ulcers with a similar accuracy to that achieved by endoscopic assessment of 'high-risk' stigmata of recent haemorrhage (visible vessel). Moreover, the combination of a visible vessel and a Doppler positive scan appeared in this study to further improve prediction of rebleeding.

Major peptic ulcer bleeding is typically from a small (mean diameter 0.6mm) single submucosal artery just below the ulcer base which can often be identified endoscopically as a 'visible vessel' (SWAIN et al 1986a). Johnston (1984) however, has suggested that the term 'visible vessel' is a misnomer and that the endoscopic

appearance represents the nipple-like appearance of protruding clot from the breached vessel with the underlying artery being invisible. Considering rebleeding from such vessels the important factors are firstly whether an artery of significant size is involved in the ulcer base and secondly whether there is arterial blood flow in the vessel. In predicting rebleeding therefore, the ability to diagnose a patent vessel in the ulcer base may be important.

With the advent of urgent endoscopy the predictive value of stigmata of recent haemorrhage was first identified. Although studies have confirmed the prognostic significance of the 'visible vessel' there remains considerable variation in the rebleeding rate of such lesions between 32-100% (GRIFFITHS et al 1979; STOREY et al 1981; MacLEOD et al 1982; WARA 1985). Several possible reasons exist for this wide variation. There is a lack of agreement on what endoscopically constitutes a visible vessel; different studies may have detected vessels with varying success depending on the extent of ulcer base washing applied; the predictive value of a visible vessel may vary according to ulcer site (WARA 1985; SWAIN et al 1986b), a fact not often considered in published studies, and until recently the ability to diagnose a vessel in the ulcer base with pulsatile blood flow has been lacking. In this study the most accepted endoscopic definition of a 'visible vessel' as described

by Swain et al (1981) was used and a vigorous washing policy was pursued resulting in a low incidence of adherent clot in the ulcer bases.

The use of an endoscopic Doppler device to localise arterial blood flow in the upper GI tract was first described by BECKLY et al (1982). Beckly and Casebow (1986) first assessed the predictive value of a Doppler positive signal in peptic ulcer haemorrhage and found that a positive signal correctly predicted rebleeding in 73% of cases with a specificity of 95%. When visible vessels were assessed the sensitivity increased to 80% with specificity of 100%. Although forty-nine cases with various SRH were assessed, the overall rebleeding rate was only 20% with a visible vessel rebleeding rate of only 44%. Interestingly, the rebleeding rate of ulcers with fresh clot was 30% with a predictive value of a Doppler positive signal of 67% suggesting vessels may have been obscured by clot. My study in a more select high risk group of patients confirms the findings of Beckly and Casebow and also the predictive value of the visible vessel. The high rebleeding rate of visible vessels (89%) in this study may reflect our policy of vigorous washing allowing increased definition of this particular endoscopic feature. The one false positive Doppler signal in this study in an ulcer base with clot may have resulted

from inadvertent recording of a deeper vessel and the two false negatives from inadequate or incomplete probe coverage of the ulcer base.

The major drawback of endoscopic Doppler ultrasound at present is its reliance on subjective data in the form of audible signals. If Doppler ultrasound assessment is to be generally available then more objective means of confirming arterial blood flow must be developed. Direct graphic recording of the Doppler signal output has been assessed and appears to improve objectivity (RUTGEERTS et al 1988).

The ability to accurately predict which patients will rebleed is of considerable clinical importance. I have demonstrated in this study that all patients with a patent vessel in their ulcer base as identified endoscopically by visual and Doppler ultrasound criteria rebled. If this is confirmed in further studies then early therapeutic intervention by either endoscopic or surgical means may lead to an improvement in the mortality rates in these high risk patients.

CHAPTER 10

ALTERATION OF REBLEEDING RATES BY ENDOSCOPIC THERAPY

10.1 INTRODUCTION

The most important adverse prognostic factor in patients admitted with peptic ulcer haemorrhage is continuing bleeding or rebleeding (COGHILL and WILLCOX 1960; SCHILLER et al 1970; JONES et al 1973). Although this group may constitute only 20% or less of all upper GI bleeding cases they present a major therapeutic challenge (ALLAN & DYKES 1976).

Medical therapeutic regimes in peptic ulcer haemorrhage using acid inhibitory agents (COLLINS and LANGMAN 1985), synthetic vaso-inhibitory GI hormones (SOMERVILLE et al 1985), antifibrinolytic agents (BARER et al 1983) or mucosal protective agents (RASKIN et al 1985) have shown no convincing evidence of benefit. Although surgery has established efficacy in terms of control of bleeding or rebleeding (READ et al 1965; MORRIS et al 1984), with an increasingly elderly population surgery as the sole therapeutic manoeuvre is likely to be accompanied by an unacceptable morbidity and mortality. Endoscopic therapy in contrast carries a low morbidity and has the advantage of potential combination with the diagnostic endoscopy. Although endoscopic treatment of bleeding peptic ulcers is at present the most promising therapeutic modality, only a few studies assessing thermal (RUTGEERTS et al 1982; MacLEOD et al 1983; SWAIN et al 1986c; LAINE 1987), or injection techniques (PANES et al 1987; CHUNG et al 1988), have

shown convincing evidence of improvement in terms of reduced rates of rebleeding, surgery or overall mortality. In addition, several other studies using similar techniques have failed to show any benefit (ROHDE et al 1980; IHRE et al 1981; ESCOURROU 1981; KERNOHAN et al 1984; GOUDIE et al 1984; KREJS et al 1987; BREARLEY et al 1987b). There remains therefore a need for improved endoscopic techniques with each being carefully assessed in controlled clinical trials. Of the currently available thermal methods, the heater probe developed by David Auth in Seattle in 1978 has been shown in experimental studies to be the safest and most effective in producing vessel coagulation (PROTELL et al 1978; SWAIN et al 1984; JOHNSTON et al 1987).

I have recently completed a prospective, randomised, controlled study assessing the efficacy of heater probe therapy in bleeding peptic ulcers.

10.2 PATIENTS AND METHODS

All patients admitted to the Western Infirmary, Glasgow with acute upper GI haemorrhage over the 16 month period of the trial (August 1986 - November 1987) were considered for inclusion. Patients presenting with haematemesis and/or melaena were routinely endoscoped within 24 hours of admission by an experienced member of the Haematemesis Management Team (HMT). Potentially eligible patients were diagnosed endoscopically to have:

a) a single peptic ulcer in the stomach, pyloric canal or duodenal cap.

b) no other significant upper gastrointestinal source of blood loss such as oesophageal varices, carcinoma or multiple bleeding erosions.

When a patient was recognised to be potentially eligible for study entry the ulcer was assessed by the Heater Probe endoscopist (myself). The patient was only deemed eligible for entry into the study if the following criteria were also met:

a) actively bleeding sites on the ulcer before or after washing and/or

b) a visible vessel in the ulcer base before or after washing and

c) confirmed accessibility of the heater probe to the source of blood loss.

Active bleeding was defined as a continuous flow of blood from the ulcer base continuing for the duration of the endoscopy. A visible vessel was defined as an elevated red or blue spot, a pulsatile pseudoaneurysm or active arterial spurting. These endoscopic criteria are known to be associated with the highest risk of rebleeding (FOSTER et al 1978; GRIFFITHS et al 1979; STOREY et al 1981).

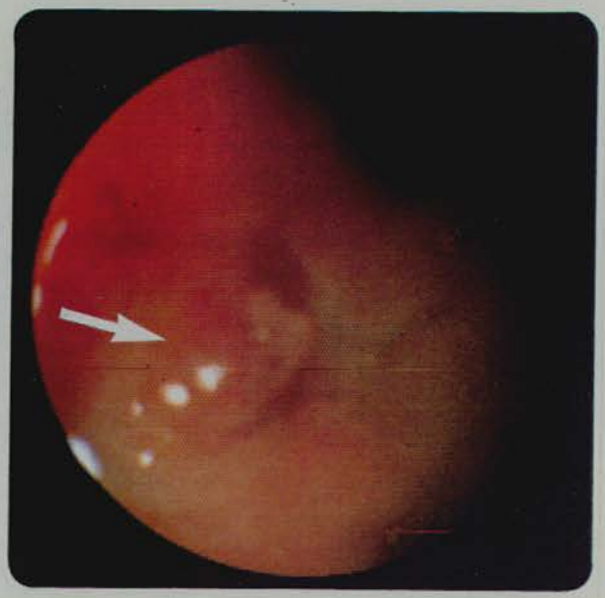
Patients who fulfilled these criteria were then stratified for age (<60, >60), shock (systolic BP < 100, pulse > 100: present/absent on admission) and ulcer site

(GU/DU). Randomisation was carried out within each group, a sealed envelope being opened to indicate either heater probe (HP) or sham therapy.

HP therapy was applied by a single operator (myself) using an Olympus GIF-IT10 endoscope and Olympus Heatprobe Unit (HPU) CD 10Z (3.7mm diam). The HP technique applied was that recommended by Johnston (JOHNSTON et al 1985). With active haemorrhage the HP was used to tamponade the bleeding point until haemostasis was achieved. The HP, through its proximal water ports, allowed continuous washing during tamponade which helped to indicate when haemostasis had been successful. The HP was then activated at the 25 joule setting and further therapy applied until complete haemostasis was secured. In the absence of active bleeding, a clot overlying an ulcer was washed until the underlying bleeding point or visible vessel was seen. Following this cautery was applied as described above (Fig.34). On average 7 HP applications/patient delivered at 25-30 J setting were required to achieve complete haemostasis. Sham therapy consisted of the HP being held inactivated in the gut lumen. Only the HP endoscopist was aware of which treatment each patient had received and he took no further part in their management.

Following endoscopy patients were managed by members of the HMT unaware of the initial randomisation and their progress documented until discharge or death. All

a



b

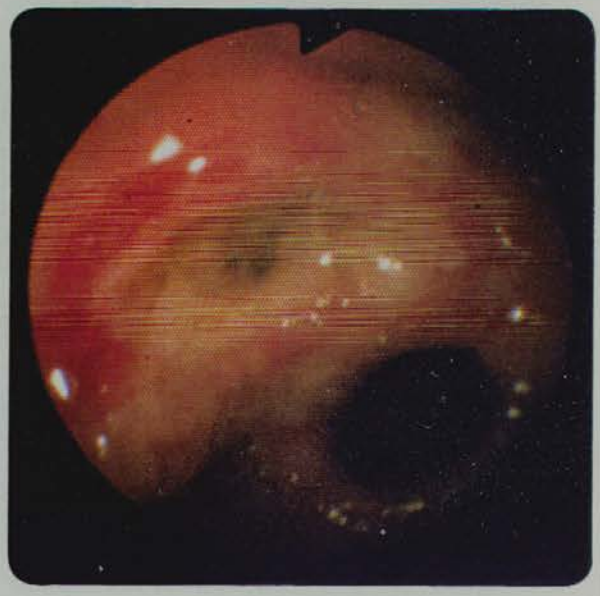


FIGURE 34

Visible vessel in pre-pyloric gastric ulcer base (a) before and (b) after 6 x 25J heater probe applications. The black spots after therapy represent the coagulated vessel.

patients received H2 receptor antagonist therapy (Ranitidine 50mg IV 6 hourly) and blood transfusion where deemed appropriate by the attending clinician. Rebleeding was diagnosed by HMT members if one of the following features was present.

a) fresh blood in the upper gastrointestinal tract (UGIT) at re-endoscopy or surgery.

b) vomiting fresh blood at any time other than immediately after endoscopy where fresh blood had been noted in the UGIT.

c) fresh melaena plus <u>one</u> of the following:

   1. haemodynamic and clinical evidence of hypovolaemic shock (systolic BP < 100, pulse rate > 100)
   2. a falling Hb despite blood transfusion (failure to raise Hb by more than 0.5g/dl per unit of blood transfused).

Surgical intervention for haemostasis was undertaken when deemed appropriate by the attending HMT surgeon.

Quantitative data (expressed as Mean ± SEM) was analysed by the unpaired, two-sided Wilcoxon Rank Sum Test. Integral data was compared by the Fishers exact test. Significance was taken at the 5% level ($p \leq 0.05$).

All patients gave written, informed consent and the study was approved by the local hospital Ethical Committee.

10.3 RESULTS

During the 16 month trial period (August 1986 - November 1987) 630 patients presenting with suspected acute upper gastrointestinal haemorrhage were endoscoped within 24 hours of presentation to the Western Infirmary, Glasgow. One hundred and sixty six (26%) were found to have a peptic ulcer. One hundred and fifteen (69%) had either no stigmata of recent haemorrhage (SRH) or minor SRH (flat black/red spots) at the time of endoscopy. This group was deemed a low risk group in terms of rebleeding but their progress was also documented until discharge. None of these patients rebled. Fifty one patients had a single peptic ulcer with either active haemorrhage or a visible vessel and 43 were entered into the trial. There were 8 exclusions; 4 high lesser curve gastric ulcers were inaccessible to endoscopic treatment and were therefore not randomised; the HP endoscopist was not available for 2 patients; in 1 patient there was torrential arterial haemorrhage from a posterior wall DU necessitating immediate surgery and in 1 patient the attending surgeon had decided on immediate surgery following endoscopy and therefore this patient was not randomised. Of the 4 patients excluded because of inaccessibility, 4 rebled, 3 required emergency surgery for haemostasis and 2 died.

Of the 43 patients entered into the trial 20 were randomised to receive HP therapy and 23 sham therapy. Both groups were well matched with regard to clinical and endoscopic criteria known to influence prognosis (Table 18).

TABLE 18

CLINICAL AND ENDOSCOPIC CHARACTERISTICS OF THE STUDY GROUPS

	SHAM (n = 23)	HP (n = 20)
Age	53.0 ± 5.0	57.0 ± 4.0*
Admission Hb (gdl)	11.0 ± 2.5	10.0 ± 2.7
Pre-treatment blood transfusion (units PCC)	1.2 ± 1.3	1.2 ± 1.3
Ulcer Site		
GU	7	8
DU	16	12
Endoscopic Features		
Active oozing	19	13
Bleeding vessel	2	5
Non bleeding vessel	2	2

*Clinical entry characteristics are given as Mean ± SEM

In patients actively bleeding at the time of endoscopy immediate haemostasis was achieved in 14/18 (78%) HP treated patients compared with 0/21 following sham treatment ($p<0.0002$). The post treatment blood transfusion requirements (units packed cells) were 1.7 ± 0.4 (mean ± SEM) in the HP group and 2.8 ± 0.6 in the sham group. Mean non-operative hospital stay (days) was 4.1 ± 0.2 (mean ± SEM) in the HP group and 4.4 ± 0.4 in the sham group. No rebleeding occurred in the HP treated group (0/20) while 5/23 (22%) of the sham treated group rebled ($p = 0.05$). Surgery for haemostasis was required in 3/5 of the sham treated patients who rebled. No HP or sham treated patients died.

When endoscopic characteristics were assessed, 0/7 ulcers with visible vessels rebled in the HP group while 3/4 rebled in the sham treated group. Considering all untreated ulcers with a visible vessel in the study, 7/8 (88%) rebled compared with 0/7 following HP therapy ($p<0.04$). In ulcers with active oozing 0/13 rebled in the HP group while 2/19 rebled in the sham group.

One perforation occurred 3 hours following HP treatment in a 76 year old male patient who had an actively bleeding anterior wall DU. He had a prolonged endoscopy and had a total HP application of 250J. At laparotomy a clean acute anterior duodenal perforation was

noted with no macroscopic evidence of thermal induced perforation. A truncal vagotomy and pyloroplasty was performed and he made an uncomplicated recovery.

10.4 DISCUSSION

This study has demonstrated that heater probe therapy reduces rebleeding rates in patients presenting with acute upper GI haemorrhage from peptic ulcers with endoscopic criteria suggesting a high risk of rebleeding. As expected no significant differences in requirements for surgery or mortality rates were seen due to the relatively small numbers involved.

As the population presenting with acute upper GI haemorrhage ages, there is a need for a simple, inexpensive and effective endoscopic therapy for peptic ulcer haemorrhage. Endoscopic injection therapy with adrenaline and polidocanol (PANES et al 1987)or adrenaline alone (CHUNG et al 1988) have recently been used to treat ulcer haemorrhage and have shown convincing benefit in producing immediate haemostasis and reducing the requirement for emergency surgery. Further controlled studies assessing these treatment regimes are however required to confirm these findings.

The heater probe (HP) is small, portable and relatively inexpensive. In addition, it has specific technical advantages over other currently available endoscopic thermal devices. Firstly, it has a powerful

washing facility which, by improving visibility, allows accurate targetted therapy directly onto the bleeding site. Secondly, the HP produces coagulation by combining heat and pressure simultaneously (coaptive coagulation). This results in more effective haemostasis with less tissue erosion than with laser photocoagulation which requires tissue heating alone to induce vessel shrinkage (zonal heating) due to the considerable thermal energy lost in flowing arterial blood (JOHNSTON et al 1987) (Fig. 35 A & B). Thirdly, the HP, unlike other thermal devices, can be applied and activated tangentially allowing better access to difficult ulcers. Disadvantages encountered with the HP are few although with any device requiring physical pressure to produce vessel tamponade there is always the risk, albeit small, of visceral perforation. Several experimental studies however, have confirmed the HP to be the safest and most effective thermal device currently available (PROTELL et al 1978; SWAIN et al 1984; JOHNSTON et al 1987).

The results of this study differ from a preliminary report by Matthewson and his colleagues where laser but not HP showed a benefit over controls (MATTHEWSON et al 1987). The studies, however, are not entirely comparable in that their randomisation was biased towards HP therapy and in addition data from previous laser work was recruited to improve the significance of laser over HP treatment. A previous uncontrolled study by Johnston et

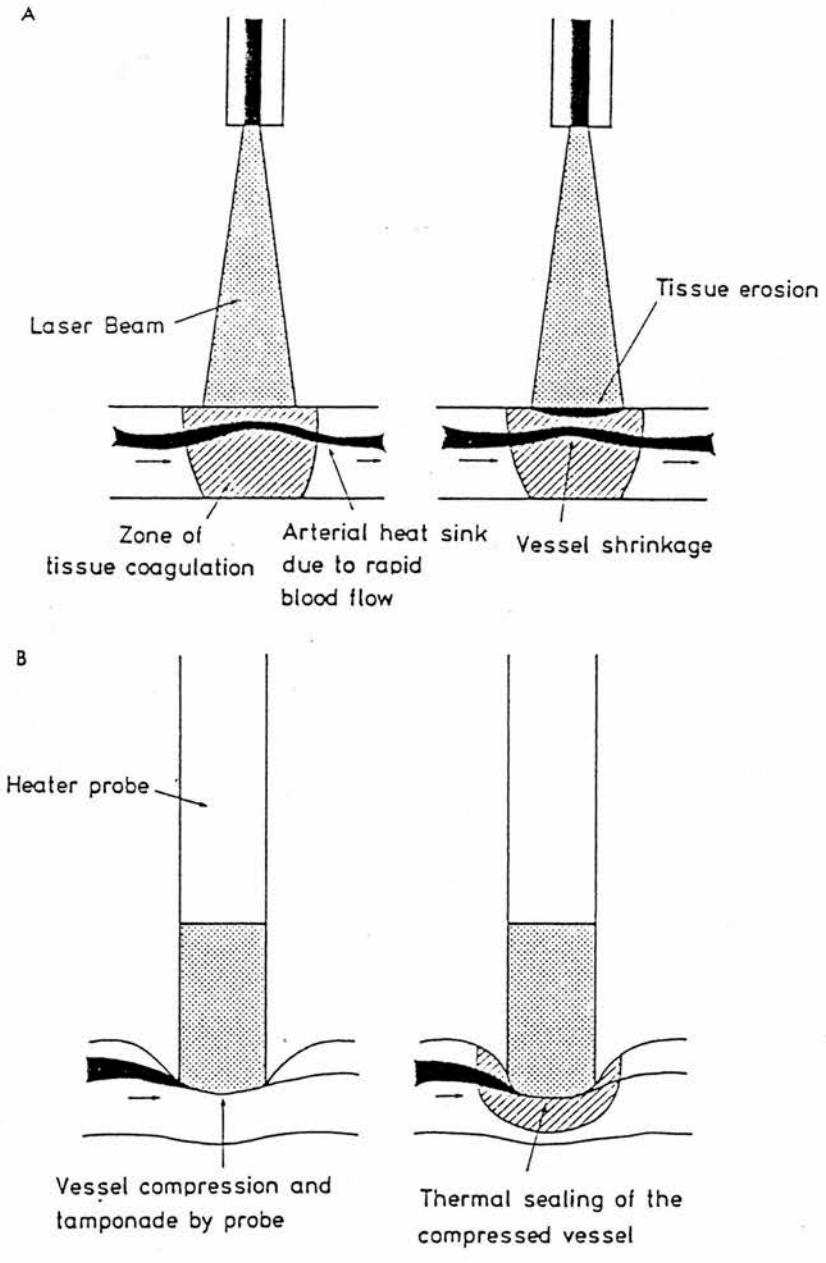


FIGURE 35 Diagramatic representation of arterial coagulation by (a) zonal heating and (b) coaptive coagulation.

a) Section through intestine wall demonstrating submucosal artery with Nd-YAG laser beam applied. The laser produces deep tissue penetration but only minimal vessel shrinkage due to 'heat-sink' effect of flowing arterial blood. With increasing power the artery is coagulated however surface tissue erosion and deep tissue penetration have occurred.

b) The heater probe is applied with moderate force (50G) to tamponade the underlying submucosal artery. With the vessel occluded, the heater probe is activated to seal the vessel. After HP treatment a deep impression remains in the mucosa but with less tissue erosion than after laser treatment.

al (1985) showed the HP to be more effective than the Nd-YAG laser in producing haemostasis. Furthermore, recent uncontrolled studies have also suggested that HP therapy is highly effective in arresting peptic ulcer haemorrhage (LIN et al 1988a; LIN et al 1988b).

In evaluating new endoscopic therapeutic methods in upper GI haemorrhage it is important to identify and study only patients at high risk of rebleeding, where benefit from an interventional treatment regime may be seen early. This study evaluated only patients who were either actively bleeding or who had visible vessels, both 'high risk' factors in predicting rebleeding (GRIFFITHS et al 1979; WARA 1985). In this study the rebleeding rate of untreated visible vessels was 88% confirming the significance of this endoscopic feature. In contrast no rebleeding was noted in the 7 visible vessels treated with the HP emphasising the efficacy of the HP in treating these lesions.

The high rebleeding rate of the 5 inaccessible high lesser curve gastric ulcers is interesting. Evidence exists to suggest that ulcer position in addition to stigmata may be important in prediction of rebleeding (SWAIN et al 1986b). Ulcers which lie in close proximity to major vessels particularly high lesser curve gastric ulcers (left gastric artery) and postero-inferior duodenal ulcers (gastroduodenal and pancreatico-duodenal arteries) have the highest risk of rebleeding. Such ulcers

presumably may erode into arterial branches close to these main trunks and occasionally into the main vessel itself with consequent torrential haemorrhage (Fig.1). Unfortunately these ulcer sites are also the most inaccessible and difficult to treat endoscopically, a problem which has been encountered in previous series (MacLEOD et al 1983; SWAIN et al 1986c; BREARLEY et al 1987b; KREJS et al 1987).

Endoscopic thermal coagulation with the heater probe can therefore produce immediate haemostasis (endostasis) and reduce the incidence of rebleeding in major peptic ulcer haemorrhage.

CHAPTER 11

OVERVIEW AND FUTURE AREAS OF RESEARCH

This thesis has attempted to improve our knowledge of the pathophysiology of upper gastrointestinal haemorrhage. In particular I have endeavoured to explain the paradox that the majority of upper GI bleeds should stop spontaneously despite the hostile local environment.

The discovery that simulated duodenal haemorrhage should produce significant inhibition of pentagastrin-stimulated gastric secretion and gastric motility suggests that locally protective physiological mechanisms may exist in the upper GI tract to promote haemostasis. The prolonged nature of this gastric secretory inhibition and the production of comparable motility changes after simulated intragastric haemorrhage supports the existence of such defence mechanisms. Moreover preliminary clinical studies have revealed increases in gastric pH following active peptic ulcer bleeding independent of any blood buffering effect which may also reflect gastric secretory inhibition. Further studies to confirm these findings are required.

The mediation of these events has been investigated both in simulated and true upper GI bleeding assessing changes in GI hormones associated with gastric secretion and motility. The significant increase in GIP concentrations seen in each group suggests that this hormone may be involved in the mediation of these inhibitory responses. Further controlled studies are warranted to investigate the effect of upper GI bleeding

on GIP release. Other possible defence mechanisms relevant to upper GI bleeding not studied in this these but worthy of assessment include alterations in gastric mucosal blood flow and changes in local mucosal haemostasis.

Current medical treatment of upper GI haemorrhage is based on inhibiting acid secretion, enhancing mucosal defence mechanisms or reducing gastric mucosal blood flow. These treatment regimes have been used without a true understanding of the physiological changes induced in the upper GI tract by haemorrhage. Confirmation of the apparent locally protective physiological mechanisms studied in this thesis may allow a more rational basis to therapy. If for example, acid secretion is already inhibited during active peptic ulcer haemorrhage, it is not surprising that the widespread use of H2 receptor antagonists in this condition have failed to improve the outcome.

Identification of the blood factor responsible for these inhibitory responses may allow the development of new forms of therapy exploiting in-built physiological protective mechanisms. A cellular or plasma based constituent may be responsible. To identify whether the inhibitory agent is present in cells or plasma the effect of intraduodenal infusion of separated cells and plasma could be studied in humans using the experimental method described in Chapter 2. There are several possible

activating factors present in blood. First, there may be a circulating factor present in plasma which is activated by contact with the GI tract to inhibit gastric secretion and motility. The ability of plasma proteins to act as a circulating source of biologically active peptide fragments activated by proteolysis from inactive precursors is a well recognised physiological control mechanism in several systems (NEURATH and WALSH 1976; REID et al 1978). The recent demonstration that biologically active peptides with neurotensin-like properties could be generated from mammalian plasma by pepsin (CARRAWAY and REINECKE 1984; MOGARD et al 1986) suggests that such plasma dependent control mechanisms may also exist in the GI tract to aid homeostasis. It seems possible therefore that intraduodenal infusion of whole blood may stimulate production of biologically active peptide fragments through proteolysis of plasma proteins which then exert acid inhibitory effects. Second, platelets contain several active metabolites including serotonin and prostaglandins (SILVER et al 1972; HOLMSEN and KARPATKIN 1986; WILLIAMS 1986) which have known acid inhibitory properties (BECH and ANDERSEN 1985; SOLL 1988). In addition, platelet-activating factor (PAF), an endogenous mediator of inflammation has been shown to reduce gastric bleeding time in rats (BERSTAD et al 1988) possibly by acid inhibition. Interestingly, if these protective responses to haemorrhage in the upper GI tract

are prostaglandin mediated then this may offer an alternative explanation for the high incidence of bleeding encountered after treatment with prostaglandin synthetase inhibitors (SOMERVILLE et al 1986). Third, blood coagulation and platelet aggregation also release serotonin, leukotrienes (SAMUELSSON 1983) and prostaglandins (SILVER et al 1972; HOLMSEN and KARPATKIN 1986; WILLIAMS 1986) all agents which have known acid inhibitory properties (BECH and ANDERSEN 1985; KONTUREK et al 1987; SOLL 1988). The secretory effects of serotonin (5HT), a peptide found in high concentrations both in the upper GI tract and platelets, however are also thought to be mediated by prostaglandins (PGE2) (RASK-MADSEN and BUKHAVE 1983; BEUBLER et al 1984). It seems possible therefore that the gastric inhibitory responses to intraluminal blood may be mediated via initiation of blood coagulation or platelet aggregation by either serotonin, prostaglandins or other arachidonic acid derivatives such as leukotrienes. In physiological terms it would seem appropriate that in the haemostatically adverse upper GI tract bleeding may induce a protective haemostatic response mediated via activation of the coagulation system. Identification of such a coagulation based inhibition of gastric acid secretion could also be performed by comparing the effect of intraduodenal infusion of fresh whole blood and fresh heparinised venous blood on pentagastrin-stimulated acid secretion.

Potential problems however may occur with this study technique particularly if the activating factor has a short plasma half-life. Endogenous prostaglandins, for example, are very rapidly metabolised in plasma to less active metabolites (MATE et al 1987).

In the present clinical situation until underlying pathophysiological mechanisms are fully understood, the identification and treatment by endoscopic means of those patients at highest risk of rebleeding is important. I have demonstrated an improvement in the ability to predict rebleeding by identifying 'high risk' peptic ulcer patients with a patent vessel in their ulcer base. In these high risk patients, endoscopic therapy by heater probe has also been shown to provide haemostasis effectively and safely.

In conclusion, protective physiological responses involving alterations in gastric secretion and motility may occur after upper GI haemorrhage to account for the high spontaneous haemostasis rate. Furthermore, early prediction and treatment of those patients in whom endogenous defence mechanisms fail may lead to more rational and effective therapeutic regimes.

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PUBLICATIONS AND COMMUNICATIONS

PUBLICATIONS

1. FULLARTON G.M., Boyd E.J.S., Crean G.P., Buchanan K., McColl K.E.L. Inhibition of gastric secretion and motility by simulated upper gastrointestinal haemorrhage - a response to facilitate haemostasis ? Gut 1988 (in press)

2. FULLARTON G.M., MacLauchlan G., Macdonald A., Crean G.P., McColl K.E.L. Rebound nocturnal hypersecretion after four weeks H2 receptor antagonism. Gut 1988 (in press)

3. MacLauchlan G., FULLARTON G.M., Crean G.P., McColl K.E.L. Regional variations in intragastric pH: a 24 hour ambulatory study in healthy volunteers. Gut 1988 (in press)

4. FULLARTON G.M., Birnie G.G., Macdonald A., Murray W.R. A controlled study of heater probe (HP) therapy in bleeding peptic ulcers. British Journal of Surgery 1988 (in press)

5. FULLARTON G.M., McColl K.E.L., Crean G.P. Effects of four weeks treatment with nizatidine on nocturnal gastric acid secretion, daytime pH and integrated gastrin respopnse. Proceedings of European Nizatidine Symposium, Brussels, November 12-13, 1987, pp 51-58.

6. FULLARTON G.M., Birnie G.G., Macdonald A., Murray W.R. Controlled study of heater probe (HP) in bleeding peptic ulcers. Gut 1988; 29: 1701.

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8. FULLARTON G.M., MacLauchlan G., Crean G.P., McColl K.E.L. Rebound nocturnal acid hypersecretion following 4 weeks H2 receptor antagonism. Gastroenterology International 1988; 1: (Suppl 1) A21.

9. Murray W.R., FULLARTON G.M. A controlled study of endoscopic heater probe (HP) treatment in bleeding peptic ulcers. Endoscopy 1988; 20 (Suppl II): 17.

10. FULLARTON G.M., Boyd E.J.S., Crean G.P., Buchanan K., McColl K.E.L. Effect of simulated upper gastrointestinal (GI) haemorrhage on gastric acid secretion and GI hormones.
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12. FULLARTON G.M., MacLaughlan G., Macdonald A., Crean G.P., McColl K.E.L. Rebound nocturnal hypersecretion after four weeks H2 receptor antagonism.
Gut 1988; 29: A1439.

COMMUNICATIONS TO LEARNED SOCIETIES

1. The effect of simulated intraduodenal haemorrhage on gastric acid secretion and GI hormones.
   British Society of Gastroenterology, London, September 18th, 1987.

2. The effect of simulated intraduodenal haemorrhage on gastric acid secretion, gastric emptying and GI hormones.
   Caledonian Society of Gastroenterology, Western Infirmary, Glasgow, November 4th, 1987.

3. Effects of simulated upper gastrointestinal haemorrhage on gastric secretion, gastric motility and GI hormones.
   Surgical Research Society, Belfast, January 8th, 1988.

4. Controlled study of the heater probe in bleeding peptic ulcers.
   Caledonian Society of Gastroenterology, Royal College of Surgeons, Edinburgh, February 12th, 1988.

5. Controlled study of the heater probe in bleeding peptic ulcers.
   British Society of Gastroenterology, Leicester, March 24th, 1988.

6. Controlled study of heater probe therapy in bleeding peptic ulcers.
   American Gastroenterological Association, New Orleans, May 17th, 1988.

7. Rebound acid hypersecretion after 4 weeks H2 receptor antagonism.
   Caledonian Society of Gastroenterology, June 3rd, 1988.

8. A controlled study of endoscopic heater probe (HP) treatment in bleeding peptic ulcers.
   VI European Congress of Digestive Endoscopy, Rome, 4-10th September, 1988.

9. Rebound nocturnal acid hypersecretion following 4 weeks H2 receptor antagonism.
   XIII International Congress of Gastroenterology, Rome, 4-10th September, 1988.

10. Rebound nocturnal hypersecretion after 4 weeks H2 receptor antagonism.
    British Society of Gastroenterology, Sheffield, September 14th, 1988.

A P P E N D I X

PROCEDURES

Gastrin Radioimmunoassay (RIA)

Blood samples for gastrin assay were added to heparinised tubes and centrifuged at 4 degrees Centigrade. The plasma was separated and stored at -20 degrees Centigrade pending assay. The antibody was raised in rabbits against synthetic human gastrin I (ICI). The antibody used in the assay 0098 was used at an approximate final dilution of 1:10,000. The antibody does not cross react with any known gastrointestinal peptides including gastric inhibitory polypeptide (GIP), gift from J. Brown; Motilin, gift from J. Brown; vasoactive intestinal peptide (VIP), gift from V. Mutt; human insulin (Medical Research Council); glucagon (Novo); natural secretin, gift from V. Mutt; except cholecystokinin-pancreozymin, gift from V. Mutt where greater than 10,000 times concentration of this material is required to produce a similar fall in bound counts as standard gastrin. The antibody also recognised Big gastrin (G34) (gift from Rehfeld) and chromatographic studies suggest that the antibody recognised not only the hepta deca peptide but also G34. The standards used are supplied by the Medical Research Council (gastrin human type synthetic 68/439). Human synthetic gastrin is iodinated by the chloramine T method. Human plasma rendered hormone free by charcoal is added to the standards in order to equilibrate the conditions between plasma samples and

standards. A charcoal separation technique is used (BUCHANAN and McCARROLL 1971). The sensitivity of the assay is 5-10 ng/l of gastrin. The assay is described in greater detail elsewhere (ARDILL 1973).

Secretin Radioimmunoassay

Plasma samples were prepared as before and stored at -20 degrees Centigrade pending assay.

Pork synthetic secretin (SG 18773, Batch ES XX1-14A, donated by Dr. Michael Ondetti, Squibb) was used for standards and labelling. Secretin was labelled with 125I (Radiochemical Centre, Amersham) by the method of Holohan et al (1973) and antibodies were raised to pork natural secretin (BUCHANAN et al 1972) (donated by Dr. V. Mutt). The antibody BB101 was used at a final titre of 1:36,000. The antibody appeared specific for secretin in that no cross-reaction was noted with pancreatic glucagon, large gut glucagon-like immunoreactivity (GLI), human insulin (MRC), gastric inhibitory polypeptide and motilin (both donated by Dr. J.C. Brown), 99% pure cholecystokinin-pancreozymin and vasoactive intestinal polypeptide (both donated by Dr. V. Mutt), or human synthetic gastrin (ICI). Extracts of human jejunum cross-reacted in the assay in an identical manner to the standards. Using a highly purified 125I secretin, a sensitivity of 6 ng/l was achieved.

Gastric Inhibitory Peptide (GIP) Radioimmunoassay

Blood samples for GIP assay were added to heparinised tubes and centrifuged at 4 degrees Centigrade. The plasma was separated and stored at -20 degrees Centigrade pending assay. The antibody was raised in sheep against porcine GIP (donated by Dr. J.C. Brown, Vancouver). The antibody (S705) was used at a final dilution of 1:600,000 in the assay tube. The iodination method used was the chloramine-T technique and the iodinated peptide purified on a SPLC system (pro or pc column). Separation of free from antibody bound hormones was by dextran coated charcoal (BUCHANAN and McCARROLL 1971). The sensitivity of the assay was 5ng/l.

Radioimmunoassay of Vasoactive Intestinal Peptide (VIP)

Blood samples for VIP assay were added to chilled heparinised tubes, centrifuged at 4 degrees Centigrade and the plasma extracted by the method of Heding (1971). The extracts were reconstituted prior to assay in 0.04 M phosphate buffer (pH 7.4). Natural porcine VIP was used for standards, immunisation and iodination. VIP (2 µg) was iodinated by the chloramine T method, the labelled hormone purified by absorption to silica and eluted into acidified ethanol. The labelled hormone was then stored at -20 degrees Centigrade in acidified ethanol. Antibodies to VIP were raised in New Zealand white rabbits, the rabbits being immunised with a conjugate of VIP to ovalbumin. Separation of free from bound hormone radioimmunoassay was accomplished by serum and dextran coated charcoal (BUCHANAN and McCARROLL 1971). The standards used were natural porcine VIP, and were prepared in an alcohol extract of plasma to mimick the unknown plasma extract sample. The assay could detect 5 ng/l with 95% certainty and was sensitive over the ranges 0-300 ng/l. There was no cross reactivity in the assay with glucagon, secretin or gastric inhibitory polypeptide and the antibody was predominantly C-terminal reactive. Further details of the assay have been reported elsewhere (ARDILL 1979).

Neurotensin (NT) Radioimmunoassay

Synthetic bovine NT (Bacham, Torrance, CA, USA) was used for immunisation, radioiodination and for RIA standards.

One mg of peptide and 2.1mg of human serum albumin (HSA) (Behringwerke AG, Marburg, FRG) were dissolved in 1ml of 0.05 M Na phosphate-buffered saline (PBS), pH 7.5. One ml of 1% (v/v) double-distilled glutaraldehyde (Agar Aids Ltd., Stansted, Essex, UK) in PBS was added dropwise with constant gentle magnetic stirring. The reaction mixture was dialysed against 2 litre of PBS for 48h. The efficiency of peptide to albumin coupling was approximately 30% as assessed by gel filtration chromatography of an immunogen aliquot after dialysis.

New Zealand white rabbits were immunised with 80 µg of coupled peptide in Freund's adjuvant (2ml) subcutaneously in the nape. Booster injections of 16 µg coupled peptide were administered at 4-weekly intervals. After 4 such boosters one animal, NT3, produced a suitable antiserum for RIA. This particular antibody was used at a final dilution of 1/90,000 in the assay tube.

Radioiodination of NT was achieved as follows: 7-10 µg of peptide were dissolved in 100 µl of 0.3 M NaH2PO4/Na2HPO4 buffer, pH 7.5, by gentle magnetic stirring. 1 mCi Na 125I (Amersham) in a volume of 10 µl was added and the iodination reaction was initiated by addition of 50 µg of chloramine-T in 100 µl 0.3 M sodium

phosphate buffer. After 15s the reaction was terminated by addition of 150 µg of sodium metabisulphite in 100 µl of 0.3 M sodium phosphate buffer. A further 200 µl of 0.3 M sodium phosphate buffer containing 200 µg KI and 20 µg HSA was added to the reaction mixture prior to purification.

Separation of unincorporated 125I and iodinated derivatives of NT was achieved by cation exchange chromatography. Separation of free from antibody bound hormone was achieved by dextran coated charcoal. The assay could distinguish 3 pmol/l neurotensin from zero with 95% confidence. Further details are given by Shaw and Buchanan (1983).

Somatostatin Radioimmunossay

Plasma samples were prepared as before and stored at -20 degrees Centigrade pending assay. The samples were reconstituted prior to assay in 0.04 M phosphate buffer pH 7.4. The standard was synthetic cyclic somatostatin (Serono). The antibody OB 5(1) was raised in rabbits to cyclic somatostatin and was used at a 1:15,000 final dilution in the assay tube. No cross reactivity with any other gut or islet peptide was found. The antibody is C-terminally directed although reaction with fragments is low, suggesting that the whole molecule is required for full cross reactivity. N-tyrosylated somatostatin (Serono) was iodinated by the chloramine-T technique and the iodinated peptide purified on a cation exchanger, (Whatman CM52) using 0.05 M and 0.25 M acetate buffer. Horse serum was charcoaled to remove endogenous peptides, extracted in an identical manner to the plasma samples, and added to the calibration samples to equilibrate conditions between standards and unknowns. Separation of free from antibody bound peptide was achieved by dextran coated charcoal. The assay could detect 3 ng/l (pg/ml) with 95% confidence. When 3 samples measuring mean values of 8 ng/l, 42 ng/l and 193 ng/l were repeatedly assayed 8 times in different batches, the coefficient of variance was 10.6%, 5.5% and 4.4% respectively.